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THE MECHANISM OF GASTRIC HYPERSECRETION FOLLOWING MASSIVE SMALL INTESTINAL RESECTION

by

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "The Mechanism of Gastric Hypersecretion Following Massive Small Intestinal Resection" submitted by Kan-Yan Chow, in partial fulfilment of the requirements for the degree of Master of Science (Surgery).

ABSTRACT

Gastric hypersecretion following massive small intestinal resection is a well-established phenomenon. Although it is generally believed to be caused by mechanisms involving either increased stimulation or decreased inhibition of gastric acid secretion, the actual underlying factor of this hypersecretion has yet to be fully explained.

Gastric hypersecretion was studied in enterectomised dogs with Heidenhain pouches. The experimental animals were divided into three groups, each subjected to a different order of operative procedures, namely: enterectomy, antrectomy, thoracic duct cannulation with lymph diversion and reinfusion. At the same time, the possibility of the loss of inhibitor(s) and the gain of gastric secretogogue(s) was examined.

It was observed that an intact antrum was essential for the production of gastric hypersecretion when a large portion of the small intestine was resected. Various findings in our experiment suggested that the production of a secretogogue(s), rather than the loss of an inhibitor(s), from the retained intestine was likely to play the major role in bringing about the hypersecretion. This secretogogue(s), which was carried in the thoracic duct lymph, appeared to potentiate and/or stimulate the antral gastrin mechanism in producing gastric hypersecretion after an extensive small intestinal resection.

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"TO BE FOND OF LEARNING IS
TO BE NEAR TO KNOWLEDGE."

\- Confucius

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INTRODUCTION

Gastric hypersecretion after massive small intestinal resection was first described by Stassoff (115) in 1914. Fifty years later, Landor and Baker (75) showed that there was a marked increase in Heidenhain pouch secretion immediately after an extensive small intestinal resection or small intestinal bypass, with an intact antral function. Their observation has been confirmed by many recent workers (96, 103, 127).

Many factors have been suggested as to the etiology of this gastric hypersecretion following massive intestinal resection. However, the bewildering cause still remains undefined despite the extensive experimental work done by numerous researchers on the subject. Different, if not controversial, views are being upheld and no one has yet offered a satisfactory explanation.

The production of a blood-borne intestinal tract gastric secretogogue was proposed by Westerheide (127) as an answer to the acid hypersecretion in small intestinal bypassed animals. He noticed that a much higher Heidenhain pouch acid output was obtained when the duodenum and upper jejunum were isolated from the intestinal stream as an intestinal loop or Thiry-Vella fistula, than when the same part of upper small bowel was excised. Though there was still gastric hypersecretion after resection of the upper small intestine in his animals, Westerheide was unable to prove that a gastric secretogogue was produced by the remaining small bowel.

Antral distension is known to bring forth gastric hypersecretion, apparently because of the increased gastrin release (81). After small intestinal resection, the possibility of delayed gastric emptying with consequent gastric stasis, which leads to gastrin release and gastric hypersecretion, has to be considered. Using radiological studies, several workers (75, 96) found that there was no gastric stasis, thus making excessive antral gastrin effects due to delayed emptying time unlikely.

Another suggestion was made by Gray et al. (37) who believed corticosteroid effects to be a cause of the increased secretion, but this view was disputed by others (22, 126).

Gastrone (14, 15), enterogastrone (73), serotonin (12, 57), secretin (38, 71), cholecystokinin (35) and bile (90) have been demonstrated to have an inhibiting effect on gastric secretion. After small intestinal resection, most of these inhibiting agents may be lost either because of inadequate absorptive surface or removal of the secretory area. Diarrhea, which is one of the complications of massive small intestinal resection (72, 99), may further aggravate the loss of inhibitory agents, and thus induce gastric hypersecretion.

Histaminase is known to occur throughout the gastrointestinal tract except for the stomach (17, 53). After massive intestinal resection, a major portion of histaminase is likely to be removed because of decreased secretory surface. This possible loss of intestinal histaminase may remove the inhibitory effect of histaminase on histamine at the parietal

cell level. Such reduction of histaminase inhibition could play a part in permitting hypersecretion, but to date no work has been done to verify that histaminase has a role in regulating gastric secretion. Antihistaminic drugs have no effect on parietal cell acid secretion unless applied directly to the mucosa, where they inhibit secretion by local toxicity.

Sillen and associates (108) believe that following massive enterectomy there is impairment of liver function resulting in failure to inactivate gastric secretogogues. Yet other workers (75, 96, 103) reported normal liver histology and normal liver functions (B.S.P. retention test, serum alkaline phosphatase, bilirubin, total protein and albumin-globulin ratio) after extensive intestinal resection in hypersecreting Heidenhain dogs. Another objection to this proposition is that the onset of hypersecretion is immediate, whereas changes in secretion due to progressive liver damage would be expected to be more gradual.

Infection as a cause of increased secretion has been postulated by Howe (60); this too has not been substantiated.

The author's interest was drawn to this problem by the work of Yakimets and Bondar (135) who observed that diversion of thoracic duct lymph markedly diminished the Heidenhain pouch acid secretion in hypersecreting, small intestinal resected animals to below the control levels. Also of interest was the clinical phenomenon that patients who had corrective operations (viz., vagotomy and antrectomy or gastrectomy) remained achlorhydric even after massive small intestinal resection (19, 30).

It was the attempt of this experiment, therefore, to determine whether gastric hypersecretion following extensive intestinal resection is caused by the loss of gastric inhibitor(s) or the production of intestinal tract gastric secretogogue(s), and to clarify the part played by the thoracic duct lymph in control of this hypersecretion.

REVIEW OF PHYSIOLOGICAL REGULATION OF GASTRIC SECRETION

The gastric secretory response to a meal was classically separated into three successive and independently operating phases (65): cephalic (vagal), gastric (antral) and intestinal. The post-prandial cutoff of gastric secretion was attributed to the withdrawal of these stimuli. Recently it is recognized that the regulation of gastric secretion is dependent upon numerous interrelated factors that result initially in stimulation and subsequent inhibition of acid output. The concept of separating the stimuli into 'phases' is incorrect, and the term 'mechanism' should be used instead. Though in an intact stomach no pure vagal, antral or intestinal mechanisms exist, for the sake of simplicity the terms vagal, antral and intestinal mechanisms in control of acid secretion are used.

I. Stimulation of Gastric Acid Secretion

A. Vagal Mechanism. In 1895 Pavlov and Mme. Schumann-Simanovskaja (97) by sham feeding of a dog, first demonstrated the stimulatory action of vagal impulses on gastric hydrochloric acid secretion. Until recently, the vagal impulses and antral gastrin were considered to operate independently in activating the HCl-secreting cells. Uvnas (123) showed in 1942 that the acid response to electrical vagal stimulation in anaesthetized cats was abolished or markedly reduced by deprivation of the antral blood supply, treatment of antral mucosa with cocaine,

or resection of antral area, and that there was a restoration of normal secretory response to vagal stimulation by infusing into the cats a histamine-free secretogogue extracted from the cats' antral mucosa. Based on his findings, it was Uvnas who suggested that vagal stimulation of gastric secretion has two components, namely a direct action on the acid secreting glands, and an indirect action by the release of gastrin from the mucosa of the pyloric antrum. It has also been shown that besides stimulating the parietal cells directly and releasing antral gastrin, the vagus also potentiates markedly the effect of all types of stimuli on the parietal cells.

The vagal mechanism is stimulated by:

(1) Psychic factor - this is well-documented since the classical 'sham feeding' experiment of Pavlov and Mme. Schumann-Simanovskaja, 1895 (97). They provided dogs with a gastric fistula and oesophagostomy, so that food swallowed never entered the stomach. On 'sham feeding' the dogs showed a secretory response of gastric juice. In hungry dogs, a similar response can be elicited from the stomach or Pavlov pouch by 'psychic' stimulation, i.e., permitting the animal to see and smell the food but not to taste it. This response to 'psychic' stimulation is promptly abolished by a small intravenous dose of atropine or by vagal section.

(2) Hypoglycaemia - when hypoglycaemia is induced by administration of insulin, in the first thirty minutes after injection there is inhibition of gastric secretion (6). The mechanism of inhibition is not known, but it does not depend

on integrity of the vagus. However, if the blood glucose is allowed to fall to about 45 mg./100 ml. or half the fasting level, strong stimulation of acid and pepsinogen secretion, lasting about ninety minutes, follows and overwhelms the inhibition. The fall of blood glucose is sensed by cells in the hypothalamus, and excitation is relayed to the stomach along the vagus nerve. The response does not occur in completely vagotomised subjects. This mode of stimulation is the basis of the Hollander's test (58) which is used to demonstrate the completeness of vagotomy.

(3) Nerve reflexes - Grossman (49) in 1960 showed that in an antrectomised dog, distension of the fundic remnant caused a moderately high secretion of acid. This effect can be abolished by vagotomy. Other workers (55, 61) have also demonstrated that reflex pathways originating in mechano- and chemo-receptors in the stomach and duodenum can cause vagal effects in the stomach.

B. Antral Mechanism. In 1905, Edkins (23) reported that acid extracts of the pyloric antral mucosa stimulated acid secretion when injected intravenously into anaesthetised cats. He suggested that the active principle, which he called gastrin, was a hormone. For over forty years following Edkins' report, there was controversy (20, 80) whether Edkins' antral extracts owed their activity to nothing more than the presence of histamine. It was not until 1948 that Grossman, Robertson and Ivy (52), using transplanted pouches, established beyond doubt that gastrin not only exists but also functions as a hormone.

In 1959, Gregory and Tracy (42, 44) devised a method for the extraction of histamine-free gastrin from hog antrum. In 1963-64, these investigators (46, 47) and their colleagues purified two gastrins, characterised them and accomplished total synthesis (2).

During the purification process, they found they had derived from the antral mucosa two almost identical peptides which they named gastrin I and II:

Gastrin I

Glu. Gly. Pro. Try. Met. Glu. Glu. Glu. Glu. Glu. Ala.
Tyr. Gly. Try. Met. Asp. Phe. NH_2

Gastrin II

Glu. Gly. Pro. Try. Met. $(Glu.)_5$ Ala. $\underset{}{\overset{SO_3H}{\overset{|}{Tyr.}}}$ Gly. Try. Met.
Asp. Phe. NH_2

The hormones exhibited identical physiological properties and differed only by the presence of a sulphate group attached in an ester linkage to the tyrosine residue in gastrin II. Each of these peptides is an extremely powerful stimulant of gastric secretion, not only in animals but also in man. However, when given intravenously in large doses, the hormones inhibit gastric acid secretion. Although the mechanism of the inhibitory action is unknown, the phenomenon has been demonstrated in dogs and rats, but not in man (84) or anaesthetised cats (32).

Besides the action on gastric acid secretion, gastrin has a wide range of other actions, which include stimulation of pepsin secretion (122), stimulation of gastro-intestinal

tone and motility (10), stimulation of pancreatic volume-flow and enzyme secretion (98) and stimulation of intrinsic factor secretion by the human stomach (63, 125).

Recently Gregory, Tracy and Grossman (48) isolated two peptides -- named human gastrin I and human gastrin II -- from human antral mucosa. These gastrins differ only slightly in their structures from the hog gastrins I and II. The structure of human gastrin I is shown below:

Glu. Gly. Pro. Try. Leu. $(Glu.)_5$ Ala. Tyr. Gly. Try. Met. Asp. Phe. NH_2

Human gastrin I differs from hog gastrin I only in that leucine replaces methionine in position five. Similarly, human gastrin II differs only in the same respect from hog gastrin II, having like the latter a sulphate group attached to the tyrosine residues. The properties of the hog and human peptides, both sulphated and unsulphated, seem to be identical quantitatively and qualitatively, so that no physiological significance can be attributed either to the very slight differences in amino acid constitution or to the presence of the sulphate group.

It is interesting to note that of the seventeen amino acid residues which comprise the total molecule of gastrin, only the C-terminal tetrapeptide Try. Met. Asp. Phe. NH_2 is required to display all of the physiological actions (122). The tetrapeptide is less potent than the total molecule; if the amide group which masks the C-terminal residue (phenyl-alanine) is removed, almost all of the activities are lost.

the molecule is the C-terminal tetrapeptide and that any substitutions found in the remainder of the chain in different species have no significant effect on physiological activity.

Many workers (71, 130) have tried to locate the cell in the antrum responsible for the production and storage of gastrin. Elwin and Uvnas (24) in 1964 reported that only traces of gastrin activity were found in the superficial part of the mucosa and in the submucosa. The highest gastrin activities were obtained from the middle 2/5 to 1/2 of the mucosa proper. However, the exact cells for gastrin formation and storage are still not defined.

The following mechanisms are known to stimulate antral release of gastrin:

(1) Vagal stimulation of the antrum - Uvnas (123) in 1942 suggested that vagal impulses were able to induce the release of antral gastrin. This was later confirmed by other workers (86). This vagal release of gastrin is an important link between the neural and the hormonal stimulation of gastric secretion.

(2) Antral distension - The release of gastrin by antral distension was demonstrated by Grossman (52) who showed that by mechanical stimulation (distension) of a transplanted antral pouch, acid secretion was obtained from a transplanted fundic pouch. He also suggested that the release of gastrin was independent of extrinsic innervation of the antrum. In 1950, Lim and Mozer (82) showed that the acid response to distension of the antrum after antroneurolysis is abolished by local

application of cocaine, by 0.25% atropine or by the injection of a ganglionic blocking agent, suggesting that mechanical stimulation releases gastrin via a cholinergic reflex within the mucosa and submucosal layer. Their results have been confirmed by Woodward et al. (129) and in addition, it has been shown that antral acidification blocks the response to antral distension (94).

(3) Contact of food with antral mucosa - Local application of meat extract and alcohol in the antrum stimulates the chemo-receptors and releases gastrin (129, 131). Acidification and local anaesthesia of the antrum inhibit the response to these types of chemical stimuli in the antrum (24, 133). Recently Schofield (1965)(104) has shown that application of 0.001% atropine inhibits the release of gastrin by meat extract in the antrum, supporting the concept of a cholinergic neural mechanism for the release of gastrin from the antrum by meat extracts.

(4) Alkaline pH of antrum - An alkaline antral pH appears to promote gastrin release (132).

C. <u>Intestinal Mechanism</u>. It was Leconte (1900)(77) who first described that food in the small intestine might stimulate gastric secretion. Later it was confirmed by the classical experiment of Ivy, Lim and McCarthy (1925)(66) who converted the whole stomach of dogs into a vagotomised 'total pouch' and restored gastro-intestinal tract continuity by esophago-duodenostomy. When their dogs were fed, the vagotomised pouch of the entire stomach started to secrete. This

response proves that gastric secretion can be stimulated by the presence of digesting food in the small intestine.

In 1941, Gregory and Ivy (40) provided dogs with fundic transplants and pouches of the rest of the stomach, with anastomosis of the esophagus to the second part of the duodenum. When these dogs were fed, both the main stomach pouch and the transplanted fundic pouch showed secretory response. They suggested that a hormonal mechanism was involved in this intestinal 'phase' of gastric secretion. In 1945 Uvnas (124) demonstrated that a gastrin-like substance was liberated from the duodenum and jejunum in response to food and mechanical distension. Lai (74) in 1964 extracted gastrin material from the duodenum of hogs and found considerable secretory responses by injecting the extracts in anaesthetised cats, whereas the extracts were inactive when injected in conscious dogs. This finding suggests that the secretory hormone from the small intestine may at least be partly due to a hormone similar to, but not identical with, gastrin from the antrum.

Gregory and Tracy (1960)(43) suggested, as in the case of antral mechanism, cholinergic excitation was an important factor responsible for effective operation of the intestinal 'phase'. They provided antrectomised dogs with pouches of the entire stomach or with denervated fundic pouches. When these dogs were fed the secretory response of the pouches was very small, but when subthreshold dosage of urecholine or carbachol was instituted, the response to feeding was much greater and occurred much sooner.

At present, very little is known about the intestinal mechanism on stimulation of gastric secretion, except that it exists and involves the liberation of a gastrin-like hormone.

D. Pancreatic Islet Cell 'Gastrin'. In the Zollinger-Ellison syndrome, a potent gastrin-like substance has been isolated from the islet cell tumors of pancreas (31, 54). However, it has not been possible to demonstrate that the pancreas can release a gastrin-like hormone under normal circumstances.

E. Histamine. Histamine is one of the most potent stimulants of acid secretion. Its action is directly on the parietal cells as shown by the fact that it can stimulate acid secretion from a gastric mucosa stripped of nerves and its action on parietal cells is resistant to atropine (69). It has been shown by Felberg and Harris (27) that a high concentration of histamine is present in the vicinity of the parietal cells. Recently Ragins (100) indicated that systemic injected histamine has a special affinity for the gastric mucosa. Another interesting fact is that histaminase is present throughout the gastro-intestinal tract except for the stomach (17). The relation of these findings to acid secretion in response to a meal is not clear, but it has been suggested that histamine may act as a final common local chemo-stimulator of the parietal cells and that it could be released locally in response to various stimuli (17).

F. Local Nerve Reflexes. In 1925 Lim, Ivy and McCarthy (81) demonstrated that distension of a denervated fundic pouch

by a balloon caused secretion of a small amount of acid. This is the result of a local nervous reflex mechanism. In 1961, Grossman (50) suggested that local nerve reflexes would potentiate the response of a gastric gland to other stimuli operating at the same time, such as the gastric hormone(s).

All the above-mentioned stimuli -- including the hormone gastrin, stimuli mediated via the vagus, cholinergic drugs and histamine -- are interpotentiated. Even a subthreshold dose of any one stimulant sensitizes the parietal cells to the effects of other types of stimuli. In this way the addition of two or more subthreshold stimuli may result in a substantial secretory response. Conversely, complete removal of a source of stimulus, as with vagal denervation, reduces considerably the sensitivity of the parietal cells to other types of stimuli.

II. Inhibition of Acid Secretion

Little is known about the inhibitory mechanism of gastric secretion. The following factors seem to be responsible for such a mechanism.

A. Inhibitory Nerve Reflexes. The autonomic nervous system is responsible for inhibitory impulses to the gastric glands. Wolf and Wolff (128) have demonstrated that emotional states such as fear and anger may inhibit gastric secretion. Leonard et al.(78) have shown that stimulation of posterior hypothalamus caused inhibition of acid secretion apparently mediated by the sympathetic nervous system, which appears to act by reducing gastric blood flow. This vasoconstriction of

the gastro-intestinal vascular bed corresponds to the observation of Abrahams (1) that extensive cardiovascular adjustments which shift blood from all other vascular circuits to the skeletal muscle bed are present during arousal of the animals by stimulation of brain stem. The recent report by Smith (112) that norepinephrine inhibited gastric acid output in conscious monkeys is consistent with the hypothesis of Leonard that vasoconstriction of the gastro-intestinal vascular bed may be the mechanism of gastric acid inhibition in their animals.

There is evidence as shown by Sircus (110) that nerve reflexes involving the vagus are partly responsible for the duodenal inhibitory mechanism, at least in its response to acid.

B. Antral Inhibitory Hormone. Ever since Pavlov's time (1910) it has been known that the accumulation of acid within the antrum and duodenum excited some autoregulatory mechanism by which further secretion of acid is inhibited. It was assumed that it was entirely due to inhibition of gastrin release either by direct local action of acid on antral mucosa or by a reflex mechanism via the vagal nerve supply to the stomach.

Harrison, Lakey and Hyde (1956)(56) in studies on dogs with divided antral pouches gave first evidence for an antral inhibitory hormone. They provided dogs with Heidenhain pouches, and also transplanted the distal half of the antrum into the colon. A continuous hypersecretion of juice occurred in the fundic pouch (and also in the main stomach) owing to continuous stimulation of gastrin release from the colonic antral implant. The remaining proximal portion of the antrum, which had been

left in situ in the stomach, and exposed to the acid secreted there, was then removed. There followed a further increase in the secretion from the fundic pouch, indicating that a source of inhibition has been removed by total antrectomy.

Recently, Thompson et al. (120) using cross-transfusion techniques, showed that gastric secretion stimulated by the intact antral-gastrin mechanism of one animal was inhibited by the infusion of blood draining the acidified antrum of another animal.

However, it still remains controversial about the existence of an antral inhibitory hormone. Many (5, 33, 94) believe that the inhibiting effects of antral acidification are caused by suppression of gastrin release.

Human and animal gastric juices have been shown to contain a gastric secretory depressant, gastrone (14, 15). It has been found that the mucous secretion of the gastric antrum has a high concentration of this gastric inhibitory substance (gastrone). The mode of action of gastrone is unknown. It has only recently been shown (8) that the depressant effect of gastrone is not due to the damage of parietal cells, nor does gastrone appear to facilitate the reabsorption of hydrogen ions from the stomach lumen.

An unexpected mechanism of inhibition of gastric secretion was reported by Gillespie and Grossman (34) who found that a single large dose of gastrin resulted in marked depression of acid secretion. The significance of this finding may well be strictly experimental.

C. Intestinal Inhibiting Hormones. It has been well documented that the presence in the duodenum of acid, hypertonic sugar, saline solutions, tap water, fat and peptone will inhibit gastric secretion (3, 4, 111). While nerve reflexes operating through the vagus may be partly responsible, hormonal factors definitely seem to play an important role. The identity of these substances is unknown, but there are strong indications that four known hormones may be involved:

(1) Serotonin - Serotonin is present in highest concentration in the duodenal and jejunal mucosa (101). Its release is promoted by intraluminal hypertonic solutions (21), acid, and distension (102). Its inhibitory action on acid secretion (12, 57) together with the recent report that serotonin antagonist is a strong stimulant for acid secretion in man (112) indicate that serotonin may play an important role in the physiological control of acid secretion.

(2) Secretin - In 1902, Bayliss and Starling (9) discovered the first hormone, secretin, which is released when the upper intestine is exposed to certain chemical substances (116) and which stimulates the secretion of pancreatic juice. Secretin has other physiological functions (117) besides its action on the pancreas. The one that this project is concerned with is its property to inhibit gastric acid secretion, which was first demonstrated by Greenlee (38) and confirmed by others (71). Though there is slight rise in serum level, it is still not known whether the serum levels of secretin attained during meals are capable of producing gastric inhibition.

(3) Enterogastrone - It is generally accepted that there exists in the duodenal and jejunal mucosa a hormone, enterogastrone, which is released by the presence of fat or its digestive products. While the main effect of enterogastrone is to inhibit gastric motility (26) it has also been shown to depress acid secretion (29). This depression would apparently act either by preventing release of gastrin from the antrum (41) or by inhibition at the parietal cell level (11).

(4) Cholecystokinin - In 1928 Ivy and Olberg (67) first described the hormone cholecystokinin, which is released by the upper intestinal mucosa when fat, fatty acids, dilute hydrochloric acid, peptone and some other substances are in contact with it (64). While the main action of cholecystokinin is to stimulate the contraction of gallbladder in its emptying of bile, it has been shown by Gillespie and Grossman (35) that it has an inhibitory effect on acid secretion. The inhibitory effect of cholecystokinin is greater than that of secretin.

III. Parietal Cell Mass

All the stimulatory and inhibiting mechanisms dicussed above act on the parietal cell of the stomach to determine whether, and to what extent, secretion will take place. Cox (18) in 1952 found by cell counts that the number of parietal cells in a normal human stomach was about one billion. Card and Marks (16) stated that the maximal acid output under conditions of maximal histamine stimulation was directly related to the size of the parietal cell mass, which may vary throughout

the life of an individual. The factors which govern the size of the parietal cell mass are unknown. Landor (76) demonstrated in dogs that physiological stimuli to gastric secretion can produce a work hyperplasia of parietal cells and, further, that degeneration of parietal cells may follow the removal of such a secretory stimulus. Clinically, it is observed that hyperplasia of parietal cell mass occurs in duodenal ulcer patients and also in patients with Zollinger-Ellison syndrome, while a significant reduction of parietal cell mass is present in gastric ulcer patients.

METHODOLOGY

I. General Outline

Adult male and female mongrel dogs weighing 14 - 30 Kg. were used. All the experimental animals were kept in the animal farm for two weeks prior to being brought into the laboratory. They were dewormed and vaccinated against infectious canine hepatitis and distemper. These dogs were fed one can of commercial dog food* per day, and water was given ad librum.

II. Plan of Experiment

The dogs were divided into three groups, A, B and C.

Group A - Seven dogs were used, each undergoing the following stages of operative procedures:

1. Heidenhain pouch construction
2. Sham enterectomy
3. Enterectomy
4. Antrectomy
5. Thoracotomy
6. Thoracotomy, cannulation of thoracic duct.

Group B - Ten dogs were used, each undergoing the following stages of operative procedures:

1. Heidenhain pouch construction
2. Antrectomy
3. Sham enterectomy
4. Enterectomy

* Dr. Ballard's

5. Thoracotomy
6. Thoracotomy, cannulation of thoracic duct.

As there was no significant change of Heidenhain pouch secretion after sham operations (sham enterectomy and thoracotomy) in the first four dogs in this group, we were satisfied that sham operations would not affect the pouch secretion. For the next six dogs in this group, we abandoned the sham operations, therefore leaving only the following stages:

1. Heidenhain pouch construction
2. Antrectomy
3. Enterectomy
4. Thoracotomy, cannulation of thoracic duct.

Group C - Four dogs were used, each undergoing the following stages of operative procedures:

1. Heidenhain pouch construction
2. Enterectomy
3. Thoracotomy, cannulation of thoracic duct.

Sham operations (sham enterectomy, thoracotomy) were not done in this group as in Groups A and B, because the author is convinced that sham operations do not affect the pouch secretion.

In Group A and Group B, the animals were subjected to the same operative procedures; the only difference between them was that in Group A enterectomy came before antrectomy, while in Group B the reverse was done. In Group C, the animals were not subjected to antrectomy, and thoracic duct cannulation was carried out after enterectomy.

III. Pre-Operative Care

All dogs were carefully examined again when they were brought to the laboratorv. If any pathology was detected, the dog would be rejected from our studies. All the experimental animals were fasted for twenty-four hours and deprived of water for twelve hours prior to surgery.

IV. Operative Procedures

After having been anaesthetized with intravenous nembutal 25 - 30 mg./Kg. body weight, the animal was intubated with an endotracheal tube. The abdomen was shaved and cleansed. The animal was then placed on the operating table, the skin prepared with Betadine solution (Nonyphenoxy, polyoxyethylene, ethanol-iodine complex) and drapes applied using sterile surgical technique. For all abdominal surgery, operations were performed through midline upper abdominal incisions, extended from xiphoid process to just below the umbilicus. Strict asepsis was maintained at all times.

Heidenhain Pouch Construction (Figure 1). The greater curvature of the stomach was held at multiple points by Babcock clamps so that the stomach would be stretched out, and the line of incision of the pouch was selected. Ligation and division of the marginal artery medial to the most medial short gastric artery was performed and a long rent formed on the adjacent omentum. An index finger was then inserted through this defect dorsal to the stomach to emerge higher on the greater curvature through the gastrosplenic ligament at the upper end of the

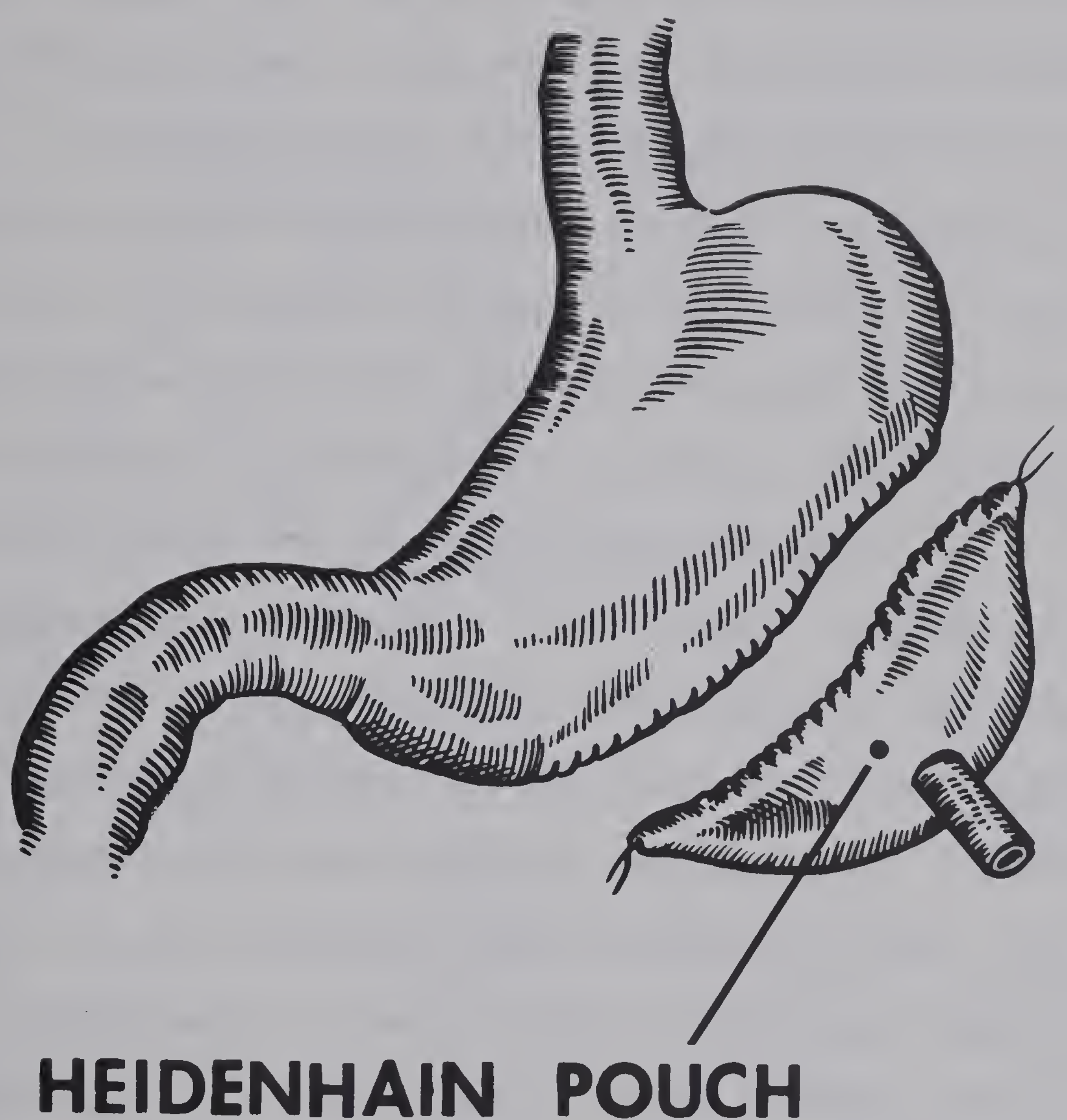


Figure 1. Heidenhain pouch

proposed line of transection. Two Allen clamps were placed into the omental gaps and were applied when the stomach was stretched and flattened. The stomach was then divided between the Allen clamps, and the cut edges of the mucosa of the main stomach and pouch were oversewn with continuous sutures of 3-0 chromic. A second running seromuscular suture of 3-0 chromic was placed over the first suture to bury the mucosal suture line. Prior to complete closure of the pouch, a stainless steel cannula was inserted through the open end of the suture line and brought out through the anterior wall of the pouch, and thence through the lateral abdominal wall.

Enterectomy (Figure 2). The small intestine was withdrawn from the abdominal cavity. Two feet of jejunum distal to the ligament of Treitz and one foot of ileum proximal to the ileocecal valve were measured with a ruler. The mesenteric vessels at these two points were cleaned of fat. The blood vessels to the part of small intestine between these two points were ligated in continuity and divided between the ligatures. Paired intestinal clamps were applied to the two areas of small intestine previously prepared, the gut divided, and the intermediate portion of the small gut removed. Restoration of gastro-intestinal continuity was by end-to-end jejunoileostomy using one layer of interrupted 4-0 silk sutures. The mesentry was then tacked together by interrupted sutures to prevent possible herniation. The intestine was replaced in the abdomen and the abdominal wound closed in layers.

Sham Enterectomy. As in enterectomy, the small intestine

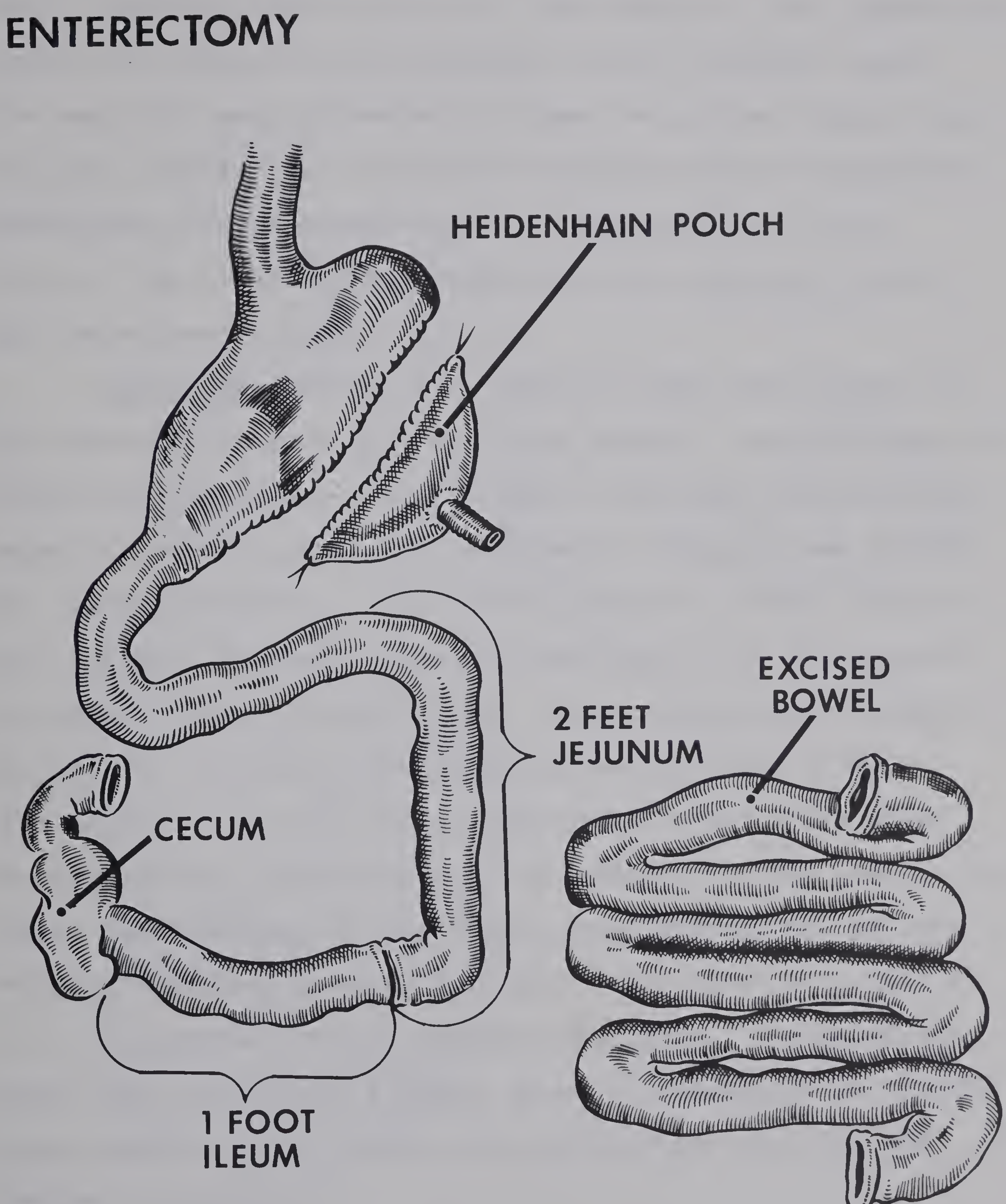


FIGURE 2. Enterectomy (65%)

was brought out from the abdomen, and instead of resecting the small intestine from a point two feet distal to the ligament of Treitz to a point one foot proximal to the ileocecal valve, the small gut was transected at these two points without ligating any vessel. The transected intestine was re-anastomosed immediately with a single layer of interrupted 4-0 silk suture. The intestine was returned to the abdominal cavity, and the abdomen closed.

Antrectomy (Figure 3). Babcock clamps were placed on the greater curvature portion of the stomach, and the organ was lifted up and forward. The arcade of the right gastroepiploic vessels along the middle of the greater curvature was divided and ligated with silk. The vessels along the lesser curvature were likewise secured. With traction applied to the greater curvature, using several Babcock clamps, a point at the mid portion of the greater curvature was selected for division. This point was usually just to the right of the first short gastric artery. A similar site was selected on the lesser curvature just proximal to the midway point between the pyloric vein and oesophago-gastric junction. This point was usually 2 - 3 cm. proximal to the incisura angularis. The angularis itself was not used as a guide, since it represents an inconstant landmark which varies with peristaltic acitivity and changes in posture.

Two clamps were placed at right angles to the long axis of the stomach along the greater curvature at the previously selected site. This portion of the stomach, about one-third

ANTRECTOMY

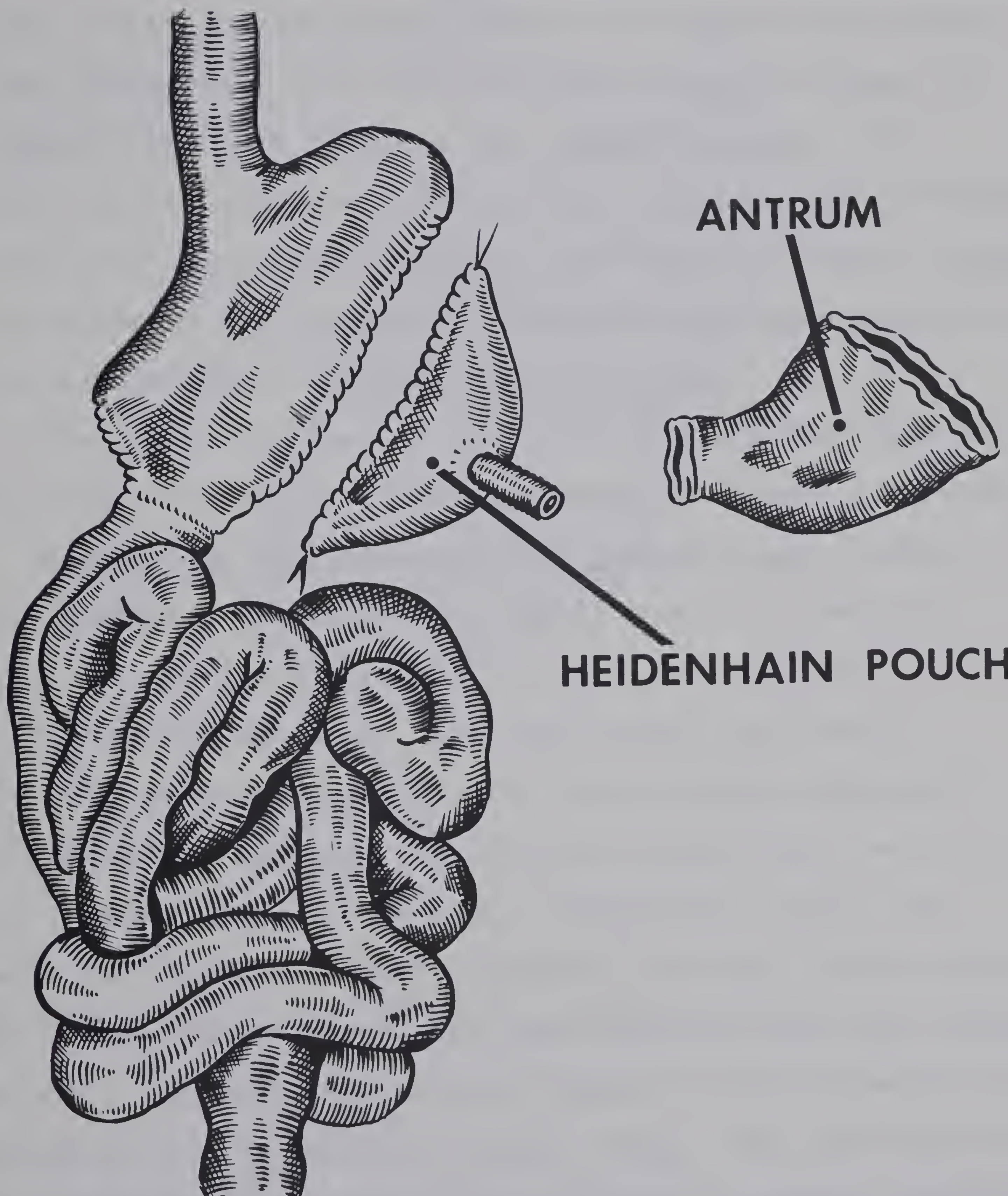


FIGURE 3. Antrectomy with end-to-end gastroduodenostomy.

of the width of the organ, was then divided. From this point of division, straight clamps were placed obliquely along the lesser curvature up to the point previously selected for division. This portion of the lesser curvature of the stomach was then transected, and closed with two inverting layers of 2-0 chromic gut, thus making a new lesser curvature. The antrum, together with the pylorus, were then removed by dividing the first part of duodenum between the clamps, and gastro-intestinal continuity was achieved by end-to-end gastroduodenostomy using a single layer of continuous 2-0 chromic.

The excised antrum was then sent to the pathologist for histological examination to confirm complete removal of antrum.

Thoracotomy and Cannulation of Thoracic Duct (Figure 4). All the dogs were intubated with McGill tubes for positive pressure ventilation and placed on their left side to aid a right thoracotomy exposure. The right chest was entered through the tenth intercostal space, and exposure maintained by retraction and packing. By carefully separating the parietal pleura from the aorta in the right costophrenic angle, the thoracic duct could be located lying to the right of the aorta in the fatty areolar tissue. At this point the duct was opened and a small silastic cannula was inserted to pass beneath the diaphragm and lie within the cisterna chyli. The duct proximal to the insertion of the cannula was ligated to ensure complete diversion of lymph to the cannula. A tie was also placed around the duct and cannula and secured to the pleura. The distal or free end of the cannula was then threaded through the diaphragm

THORACIC DUCT CANNULATION IN RIGHT CHEST

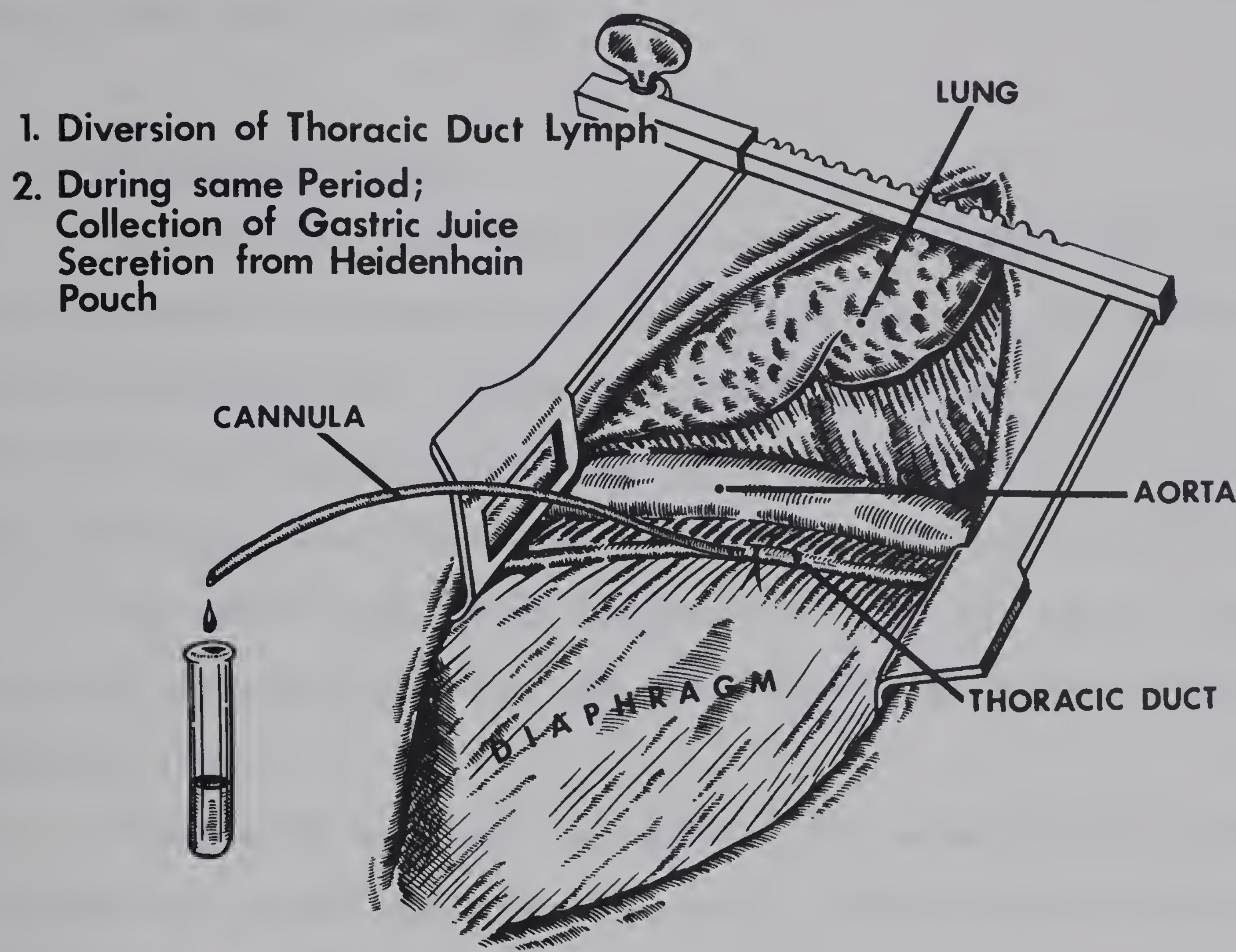


Figure 4. Right thoracotomy and cannulation of the thoracic duct with lymph diversion. (diagramatic)

and out through a metal cannula on the side of the abdomen. The metal cannula served to protect the silastic cannula from being chewed off by the dog.

V. Post-Operative Care

During the first three post-operative days, hydration was maintained by means of 30 cc./Kg. of 5% dextrose saline given subcutaneously. After the third post-operative day, water, then milk and pablum were given as tolerated. By the sixth post-operative day, most dogs were able to resume normal feeding.

For those dogs which had resection of the small intestine, 1 gm. of calcium carbonate was given orally each day to minimize diarrhea (79).

After each surgical procedure, the animals were allowed a minimum of three weeks for recovery, at the end of which time pouch secretions were collected.

During the control phase as well as four weeks after enterectomy, haemoglobin, total protein, albumin-globulin ratio and Bromsulphalein (B.S.P.) retention tests were measured in each dog. Radiological gastric emptying time by barium meal study was carried out before and after enterectomy.

VI. Collection of Heidenhain Pouch Secretion

The Heidenhain pouches were fitted with metal cannulas which drained into rubber bladders.* Twenty-four hour and eight-hour, hourly fasting and post-prandial secretions were

* Bard rubber bladder

collected. All dogs were fasted for 12 hours before the collections.

The twenty-four hour collections were carried out in the vivarium under normal conditions of activity. The bladders were put on at 9:00 a.m. while the Heidenhain pouch secretions were collected at 9:00 a.m. on the following day. When the secretions were collected, the bladders were carefully checked for any damage; if leakage was detected, the collection was discarded. When post-prandial secretion was collected, dogs were given one-half tin of dog food* twice daily. During fasting collection, only food was withheld.

In the eight-hour, hourly collections, the animals were anaesthetized with nembutal (30 mg./Kg.) intravenously, and given intravenous fluid of 2/3 5% dextrose water with 1/3 normal saline solution at a rate of 50 ml. per hour. When food was given, the dogs were fed with 120 gm. of commercial dog food* homogenised with 60 ml. of water through an oral gastric tube immediately following the second collection.

VII. Collection of Heidenhain Pouch Secretion with Cannulation of Thoracic Duct (Figure 4)

Eight-hour, hourly Heidenhain pouch secretion was collected as described above. When the dog was fed at the end of the second hour, the thoracic duct was cannulated at the same time. The lymph was diverted and collected in a measuring cylinder. Five hundred units of heparin were added to the cylinder

* Dr. Ballard's

to prevent the lymph from clotting. The hourly output of thoracic duct lymph was noted and collected for three hours, at the end of which time all the diverted lymph was reinfused back into the dog. Heidenhain pouch collection was carried out hourly for another three hours.

VIII. Laboratory Procedures

1. Determination of Gastric Acidity. All the pouch secretions were measured for volume. These secretions were also titrated for free and total acid with N/10 sodium hydroxide using Topfer's reagent and phenol red as indicators. The Topfer's reagent changes from red to yellow from pH 2.9 to 4.4, then phenol red changes to red from pH 6.8 to 8.4. The titration to the first colour change (red to yellow) at pH 4 measured the amount of free acid present. From this point to the colour change with phenol red, the combined acid was titrated. The complete titration gives the amount of total acid present.

2. Bromsulphalein (B.S.P.) Determination. After sixteen hours of fasting, 5 mg./Kg. of B.S.P. dye was injected intravenously. Forty-five minutes later blood was drawn from a different limb, and dye concentration determined according to the method of Inglefinger and Bradley (62).

3. Determination of Serum Total Protein, Albumin and Globulin Levels. Total protein was done using the biuret reagents. Albumin and globulin were separated by electrophoresis on cellular acetate strip which was subjected to scanning. From the scanned strip, the total amount of albumin and globulin were

calculated.

4. Barium Meal Study. The dogs were fasted for twelve hours before the barium meal study. One hundred ml. of barium were introduced into the back of the throat of the dog with a syringe and the barium was allowed to be swallowed. X-ray studies to determine gastric emptying time were performed by making antero-posterior films hourly. Complete emptying was considered to have occurred when only traces of barium remained in the stomach.

RESULTS

In the calculation of percentage difference in the mean Heidenhain pouch secretion at different stages of the 8-hour collections, the author only used data of the last six hours (i.e., 3rd - 8th collections). Data of first and second collections were not included as these first two hours in the fasting state were necessary to allow the secretion to stabilize.

I. Heidenhain Pouch Secretion of Group A Dogs

A. Effect of Sham Enterectomy (Table I). After the control phase, sham enterectomy was performed to see if there was any effect on the Heidenhain pouch secretion. It was found that sham enterectomy brought no change to the volume, free acid or total acid in both the post-prandial and fasting states (Figures 5, 6, 7 and 8).

B. Effect of 65% Small Intestinal Resection (Table II). A 65% resection of small intestine was done on the same animals following the finding that sham enterectomy did not affect the Heidenhain pouch secretion. After the resection, a significant increase of Heidenhain pouch secretion was observed in the 24-hour post-prandial period and in the 6-hour fasting and post-prandial periods. However, there was no significant change in the 24-hour fasting secretion after enterectomy (Figure 7).

The 24-hour post-prandial Heidenhain pouch secretion showed an average increase of 63.88% in volume ($p < 0.05$), 114.53% in free acid ($p < 0.01$), and 77.36% in total acid

TABLE I

EFFECT OF SHAM ENTERECTOMY ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP A DOGS

	Control	Sham Enterectomy	Difference %	P Value
24-Hour Fasting				
Volume*	11.4	11.0	-3.39	N.S.
Free Acid†	0.4	0.3	-33.33	N.S.
Total Acid†	6.0	5.8	-2.38	N.S.
24-Hour Post-Prandial				
Volume	40.2	39.1	-2.66	N.S.
Free Acid	46.2	42.5	-7.18	N.S.
Total Acid	65.0	60.8	-6.37	N.S.
6-Hour Fasting				
Volume	3.88	2.1	-45.88	<0.01
Free Acid	16.00	2.5	-84.38	N.S.
Total Acid	58.20	53.1	-8.76	N.S.
6-Hour Post-Prandial				
Volume	8.9	7.5	-15.73	N.S.
Free Acid	168.8	142.9	-15.34	<0.05
Total Acid	278.0	258.9	-6.87	N.S.

* Volume in ml.

† Acid in mEq./L.

Mean 8 Hour Post-Prandial Heidenhain Pouch Secretion

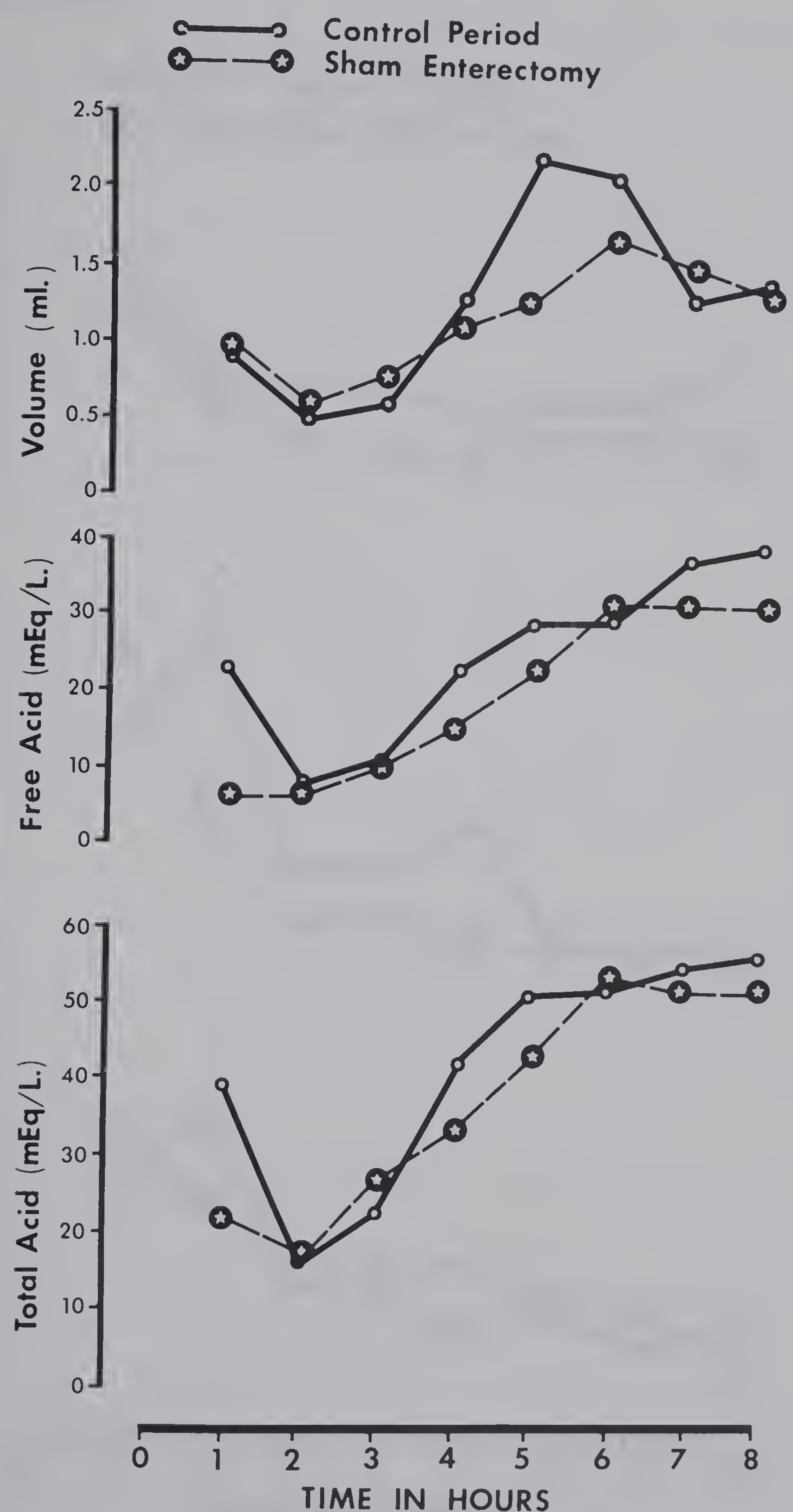


FIGURE 5. Effect of sham enterectomy on the mean hourly post-prandial H.P. secretion of group A dogs. Sham enterectomy had no significant effect on the mean volume, and free and total acids of the H.P. secretion.

Mean 8 Hour Fasting Heidenhain Pouch Secretion

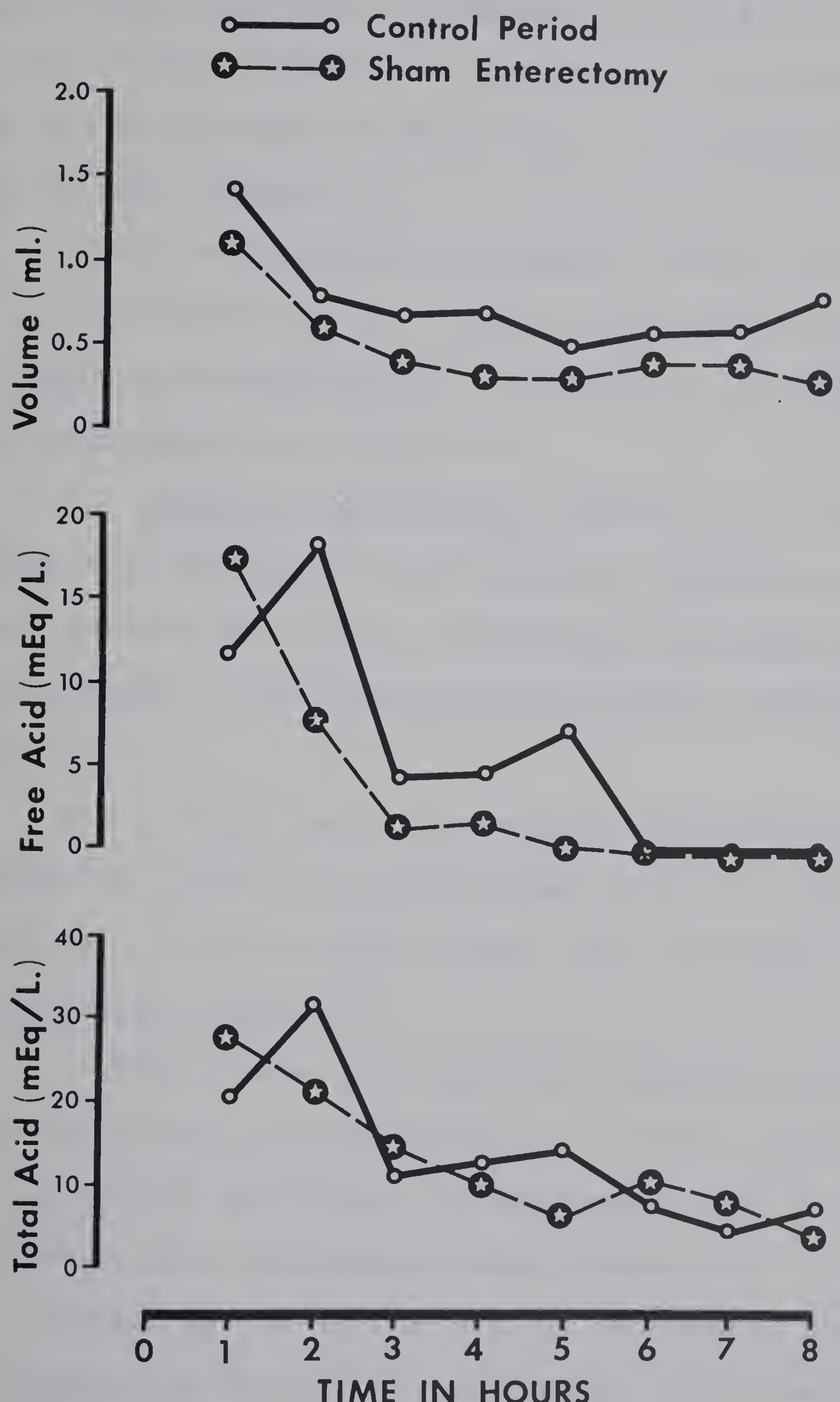


FIGURE 6. Effect of sham enterectomy on the mean hourly fasting Heidenhain pouch (H.P.) secretion of group A dogs. Sham enterectomy had no significant effect on the mean volume, and free and total acids of the H.P. secretion.

($p < 0.01$) after enterectomy (Figure 8).

In the mean total 6-hour fasting Heidenhain pouch secretion, though there was a decrease of 30.41% in the volume output ($p < 0.05$), there was a significant increase in both the free and total acids of 166.5% ($p < 0.01$) and 74.23% ($p < 0.05$) respectively (Figure 9).

There was a marked increase of 107.8% ($p < 0.01$), 149.94% ($p < 0.01$) and 89.89% ($p < 0.01$) in the mean volume, free acid and total acid respectively in the 6-hour post-prandial Heidenhain pouch secretion (Figure 10).

C. Effect of Antrectomy (Table III). A marked decrease in both the fasting and post-prandial Heidenhain pouch secretion of the 24-hour and 6-hour collections was noted when antrectomy was performed in the hypersecreting, small intestinal resected dogs.

The 24-hour fasting Heidenhain pouch secretion showed a decrease of 54.39% (non-significant [N.S.]), 100% (N.S.) and 82.61% ($p < 0.05$) in mean volume, free acid and total acid respectively (Figure 7).

In the 24-hour post-prandial Heidenhain pouch secretion, a drop of 75.11% in mean volume ($p < 0.01$), 74.93% in mean free acid ($p < 0.01$) and 56.26% in mean total acid ($p < 0.01$) resulted in this antrectomy phase (Figure 8).

Similarly, an abrupt fall of Heidenhain pouch secretion was observed in the 6-hour fasting and post-prandial collections. In the 6-hour fasting collections, a decrease of 37.04% ($p < 0.05$), 100% ($p < 0.05$) and 80.67% ($p < 0.05$) was respectively

TABLE II

EFFECT OF ENTERECTOMY ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP A DOGS

	Control	Enterectomy	Difference %	P Value
24-Hour Fasting				
Volume*	11.4	12.2	+7.28	N.S.
Free Acid†	0.4	0.3	-16.67	N.S.
Total Acid†	6.0	7.4	+91.67	N.S.
24-Hour Post-Prandial				
Volume	40.2	67.7	+68.38	<0.05
Free Acid	46.2	99.1	+114.53	<0.01
Total Acid	65.0	115.2	+77.36	<0.01
6-Hour Fasting				
Volume	3.88	2.7	-30.4	<0.05
Free Acid	16.00	42.6	+166.25	<0.01
Total Acid	58.20	101.4	+74.23	<0.05
6-Hour Post-Prandial				
Volume	8.9	18.50	+107.87	<0.01
Free Acid	168.8	421.9	+149.94	<0.01
Total Acid	278.0	527.9	+89.89	<0.01

* Volume in ml.

† Acid in mEq./L.

TABLE III

EFFECT OF ANTRECTOMY ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP A ENTERECTOMISED DOGS

	Enterectomy	Antrectomy	Difference %	P Value
24-Hour Fasting				
Volume*	12.2	5.6	-54.39	N.S.
Free Acid†	0.3	0	-100.00	N.S.
Total Acid†	7.4	2.0	-82.61	<0.05
24-Hour Post-Prandial				
Volume	67.7	16.8	-75.1	<0.01
Free Acid	99.1	24.8	-74.93	<0.01
Total Acid	115.2	50.4	-56.26	<0.01
6-Hour Fasting				
Volume	2.7	1.7	-37.04	<0.05
Free Acid	42.6	0	-100.00	<0.05
Total Acid	101.4	19.6	-80.67	<0.05
6-Hour Post-Prandial				
Volume	18.50	3.5	-81.08	<0.01
Free Acid	421.90	13.1	-96.89	<0.01
Total Acid	527.90	86.0	-83.71	<0.01

* Volume in ml.

† Acid in mEq./L.

seen in the mean volume, free acid and total acid (Figure 9).

In the 6-hour post-prandial collections, a decrease of 81.08% ($p < 0.01$), 96.89% ($p < 0.01$) and 83.71% ($p < 0.01$) was seen respectively in the mean volume, free acid and total acid (Figure 10).

D. Effect of Thoracotomy (Table IV). Lymph diversion by supradiaphragmatic thoracic duct cannulation has been shown to reduce Heidenhain pouch secretion in the hypersecreting, small intestinal resected dog. Thoracotomy was done on these enterectomised and antrectomised dogs to check the possibility that thoracotomy alone would affect the Heidenhain pouch secretion. The results revealed that thoracotomy had no significant effect on the Heidenhain pouch secretion (Figure 11).

E. Effect of Thoracic Duct Cannulation, Lymph Diversion and Lymph Reinfusion (Tables V and VI). Lymph diversion by supradiaphragmatic thoracic duct cannulation was carried out at the same time as the dogs were fed. This took place immediately after the second of the 8-hour, hourly collections. The diverted lymph was collected, the volume recorded hourly, and it averaged 40 - 50 cc. per hour. During the period of lymph diversion, despite the fact that the dogs were fed, there was a decrease of Heidenhain pouch secretion by an average volume of 86.45% ($p < 0.05$), an average of free acid of 100% (N.S.) and an average total acid of 97.55% ($p < 0.01$) as compared with the same period of the previous stage of the experiment (Figure 10).

Three hours after lymph diversion began, the collected

TABLE IV

EFFECT OF THORACOTOMY ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP A ENTERECTOMISED AND ANTRECTOMISED DOGS

	Antrectomy	Thoracotomy	Difference %	P Value
6-Hour Post-Prandial				
Volume*	3.5	3.4	-2.86	N.S.
Free Acid†	13.1	14.6	+11.45	N.S.
Total Acid†	86.0	98.2	+14.19	<0.05

* Volume in ml.

† Acid in mEq./L.

TABLE V

EFFECT OF LYMPH DIVERSION ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP A ENTERECTOMISED AND ANTRECTOMISED DOGS

	Antrectomy	Lymph Diversion	Difference %	P Value
3-Hour Post-Prandial				
Volume*	2.0	0.27	-86.45	< 0.05
Free Acid†	6.8	0	-100.00	N.S.
Total Acid†	57.2	1.40	-97.55	< 0.01

* Volume in ml.

† Acid in mEq./L.

TABLE VI

EFFECT OF LYMPH REINFUSION ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP A DOGS WITH ENTERECTOMY, ANTRECTOMY AND LYMPH DIVERSION

	Lymph Diversion	Lymph Reinfusion	Difference %	P Value
3-Hour Post-Prandial				
Volume*	0.27	0.51	+86.72	N.S.
Free Acid†	0	0	0	N.S.
Total Acid†	1.4	4.10	+192.86	N.S.

* Volume in ml.

† Acid in mEq./L.

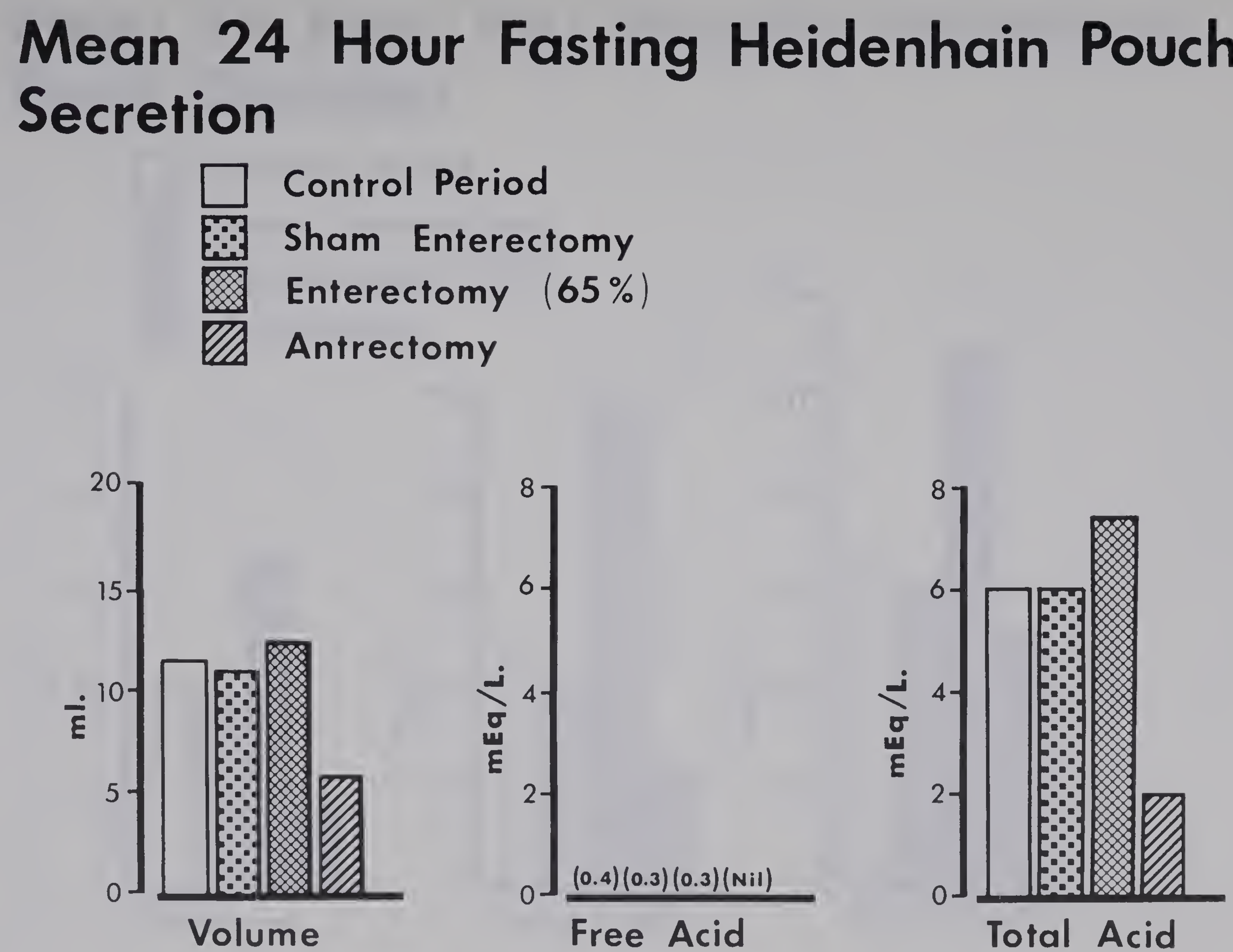


FIGURE 7. Comparison of the mean 24 hour fasting H.P. secretion of group A dogs. Both sham enterectomy and enterectomy had no significant effect on the mean volume, and free and total acids of the H.P. secretion. Antrectomy in addition to enterectomy had no significant effect on the mean volume, and free acid of the fasting H.P. secretion, but significantly decreased the mean total acid.

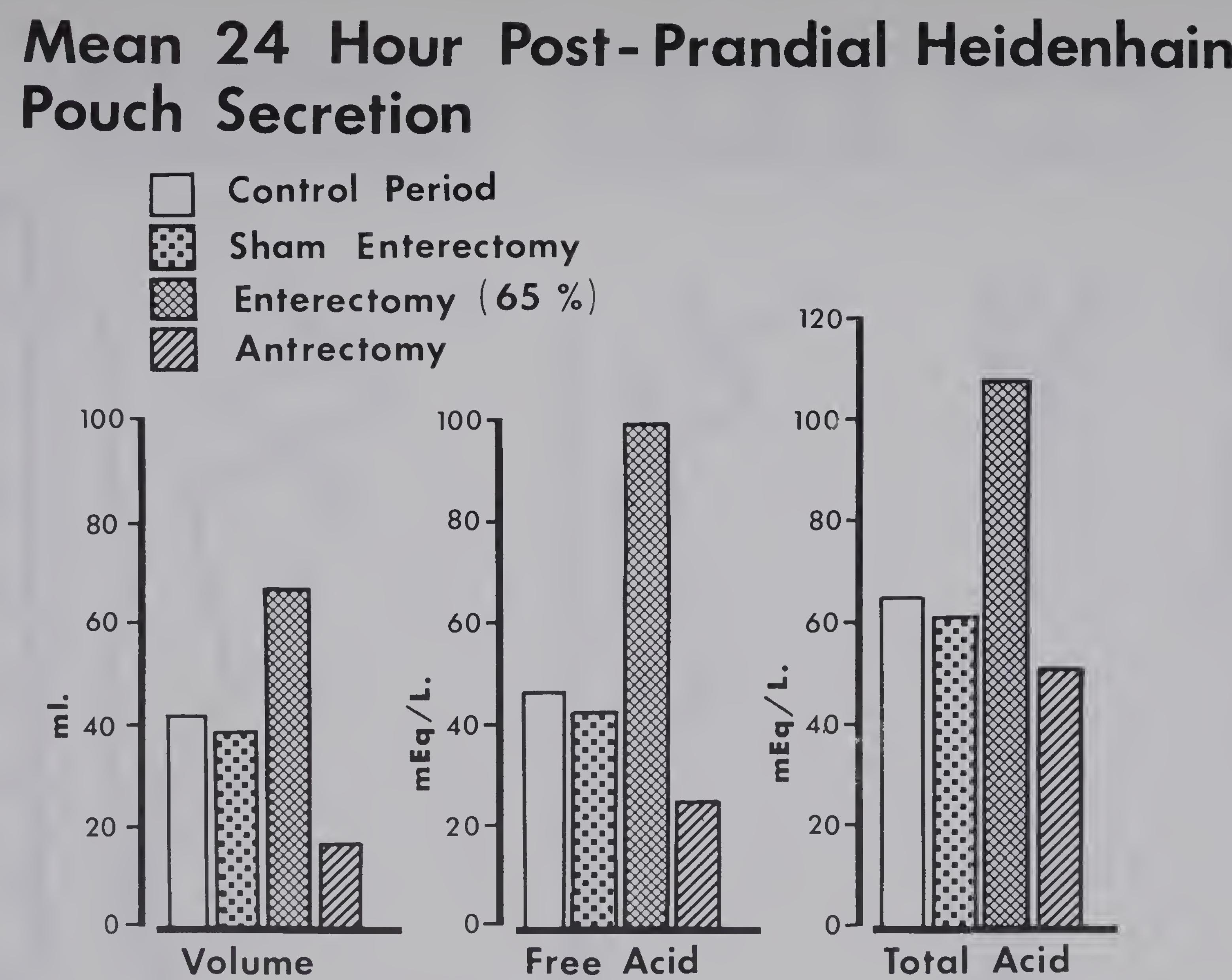


FIGURE 8. Comparison of the mean 24 hour post-prandial H.P. secretion of group A dogs. Sham enterectomy had no significant effect on the mean volume, and free and total acids, whereas enterectomy markedly increased these parameters of the H.P. secretion. Antrectomy significantly decreased the mean volume, and free and total acids in the enterectomised dogs.

Mean 8 Hour Fasting Heidenhain Pouch Secretion

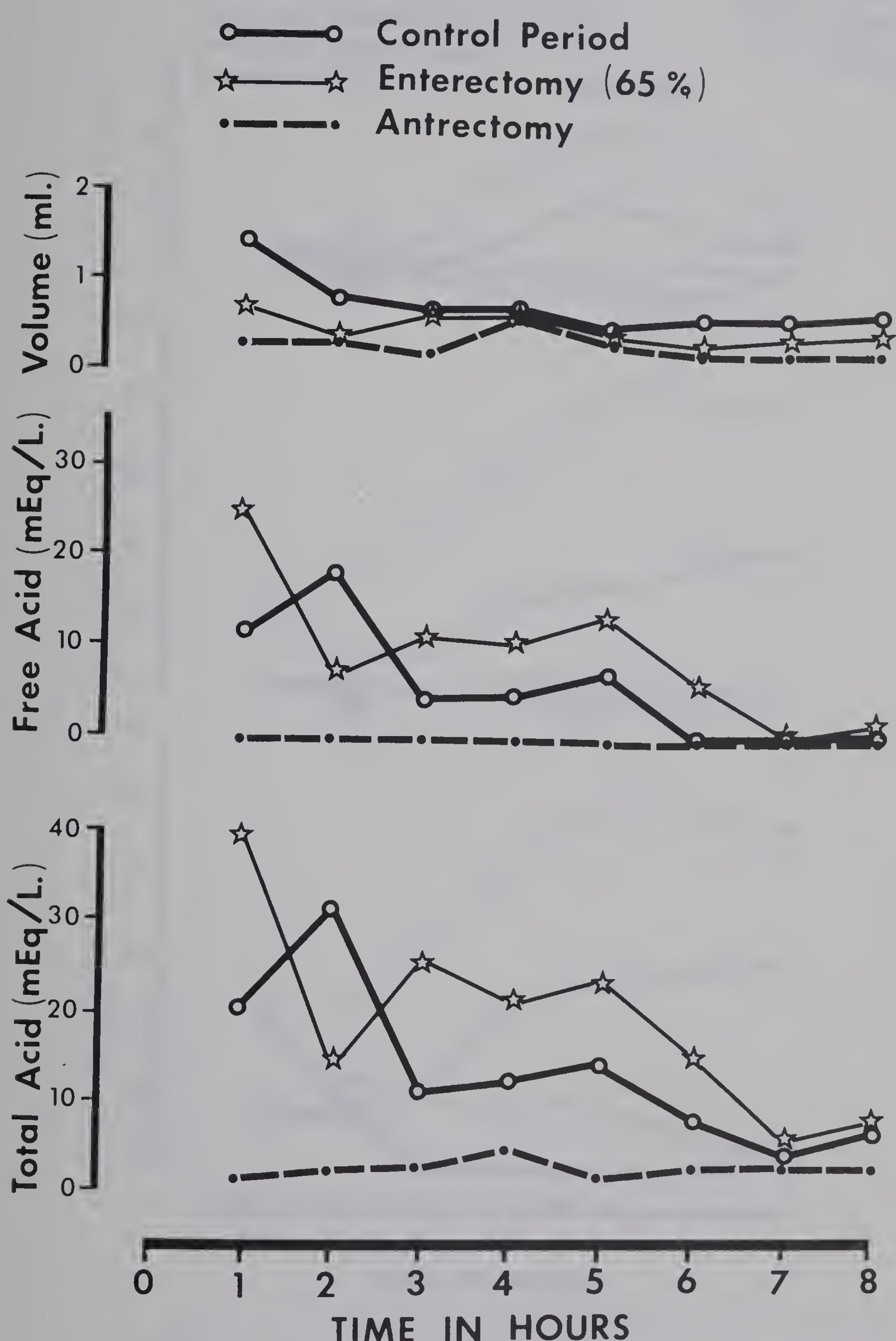


FIGURE 9. Comparison of the mean hourly H.P. secretion of group A dogs in the fasting period. Enterectomy had no significant effect on the mean volume but significantly increased the mean free and total acids. Antrectomy markedly decreased these parameters in the enterectomised dogs.

Mean 8 Hour Post-Prandial Heidenhain Pouch Secretion

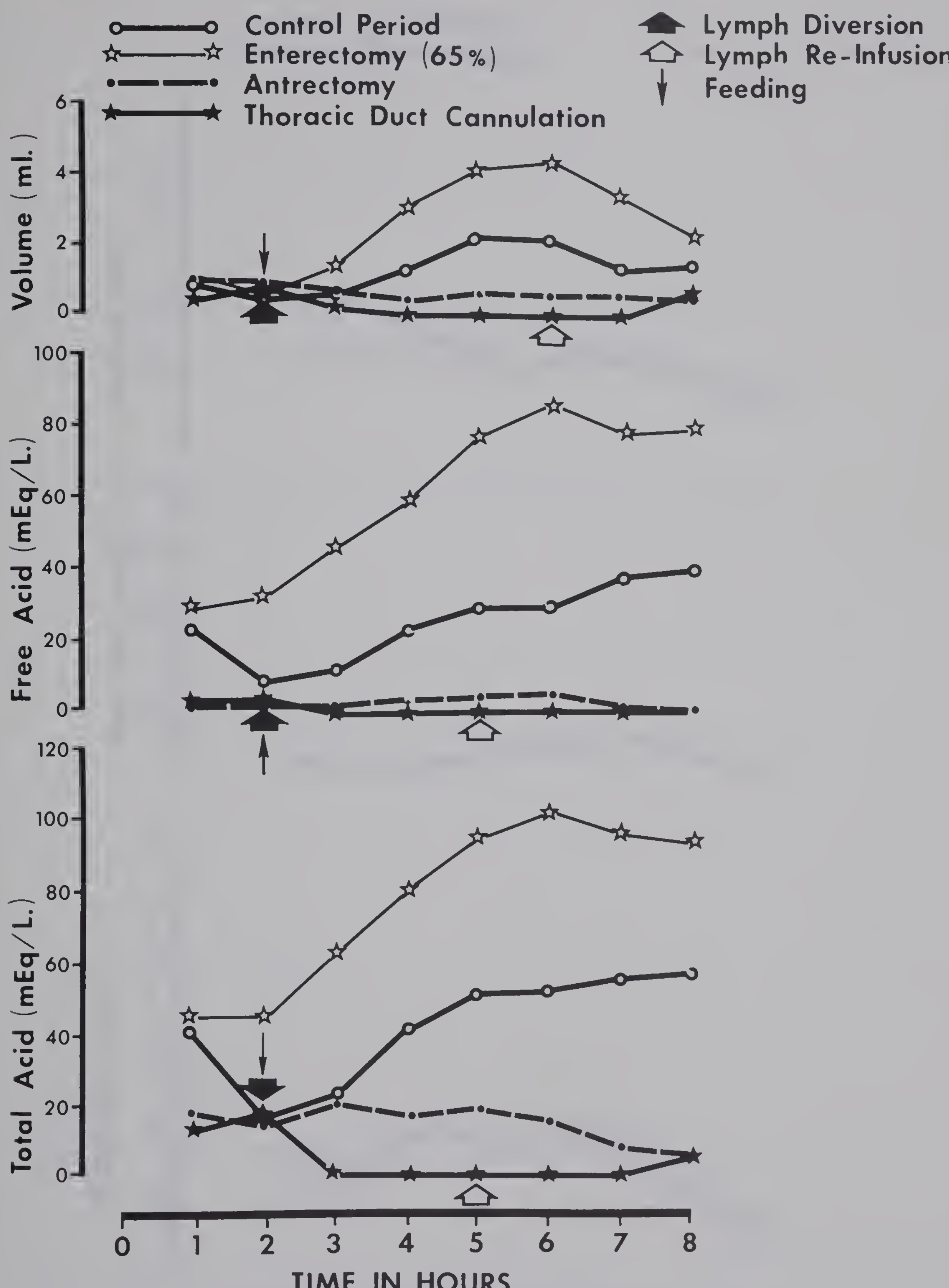


FIGURE 10. Comparison of the mean hourly H.P. secretion of group A dogs in the post-prandial period. Enterectomy significantly increased the mean volume, and free and total acids, whereas antrectomy markedly decreased these parameters in the enterectomised dogs. Lymph diversion further decreased the mean volume, and free and total acids in the enterectomised and antrectomised dogs. Lymph reinfusion had no significant effect on these parameters in dogs with lymph diversion.

Mean 8 Hour Post - Prandial Heidenhain Pouch Secretion

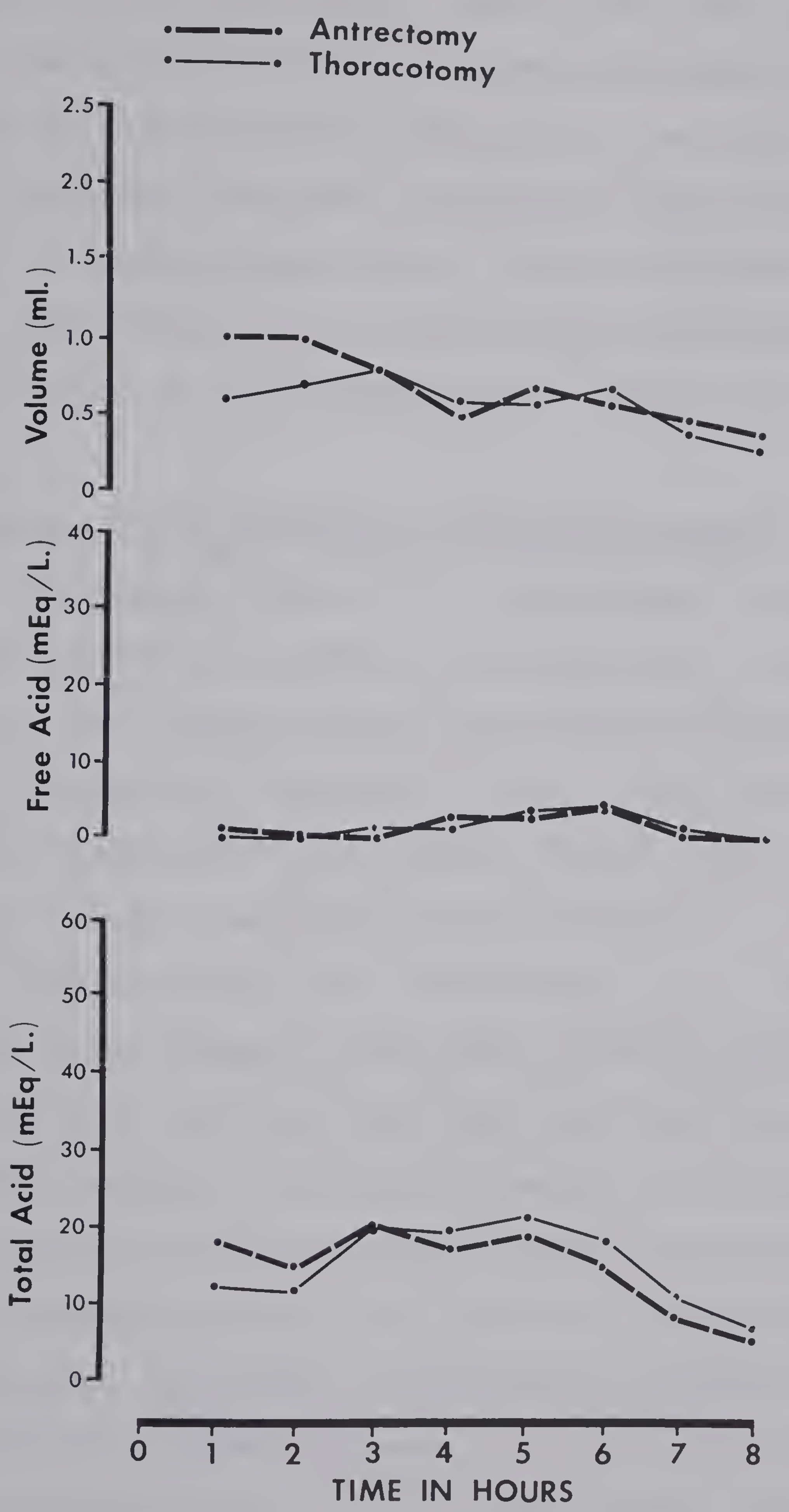


FIGURE 11. Effect of thoracotomy on the mean hourly post-prandial H. P. secretion of group A enterectomised and antrectomised dogs. Thoracotomy had no significant effect on the mean volume, and free and total acids of the H.P. secretion in these dogs.

lymph was reinfused back to the dogs over a period of three hours by the intravenous route. During the lymph reinfusion, the rectal temperatures of the dogs were recorded half-hourly. No significant fluctuation of temperature was noted. While the lymph was being reinfused, Heidenhain pouch secretion was collected for another three hours. It was observed that the Heidenhain pouch secretion in this period remained the same as before reinfusion of the diverted lymph (Figure 10).

<u>II. Heidenhain Pouch Secretion of Group B Animals</u>

A. <u>Antrectomy</u> (Table VII). Antrectomy is known to lead to a marked decrease of gastric secretion both in human beings and animals. The results of our experiments showed no exception. There was a significant decrease in the 24-hour post-prandial secretion as compared with the control phase, with a mean volume of 76.57% ($p < 0.05$), mean free acid of 82.31% ($p < 0.01$) and mean total acid of 72.19% ($p < 0.01$)(Figure 12). Though there was no significant change in the mean volume of the 24-hour fasting secretion, both its mean free acid and total acid had a significant decrease. The results were 16.36% decrease in mean volume (N.S.), 93.77% decrease in mean free acid ($p < 0.05$) and 64.77% decrease in mean total acid ($p < 0.05$)(Figure 13).

Similarly, the 6-hour post-prandial Heidenhain pouch secretion showed a marked decrease of 64.27% ($p < 0.05$), 89.19% ($p < 0.01$) and 80.15% ($p < 0.01$) in mean volume, free acid and total acid respectively in this antrectomy phase (Figure 14). However, the 6-hour fasting secretion did not have significant

TABLE VII

EFFECT OF ANTRECTOMY ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP B DOGS

	Control	Antrectomy	Difference %	P Value
24-Hour Fasting				
Volume*	27.50	23.00	-16.36	N.S.
Free Acid†	13.65	0.85	-93.77	< 0.05
Total Acid†	27.25	9.60	-64.77	< 0.05
24-Hour Post-Prandial				
Volume	139.80	32.70	-76.57	< 0.05
Free Acid	93.00	16.45	-82.31	< 0.01
Total Acid	113.80	31.65	-72.19	< 0.01
6-Hour Fasting				
Volume	10.12	5.91	-41.6	N.S.
Free Acid	58.00	17.80	-69.31	N.S.
Total Acid	131.00	54.30	-58.55	N.S.
6-Hour Post-Prandial				
Volume	25.75	9.20	-64.27	< 0.05
Free Acid	390.30	42.20	-89.19	< 0.01
Total Acid	494.78	98.20	-80.15	< 0.01

* Volume in ml.

† Acid in mEq./L.

Mean 24 Hour Post-Prandial Heidenhain Pouch Secretion

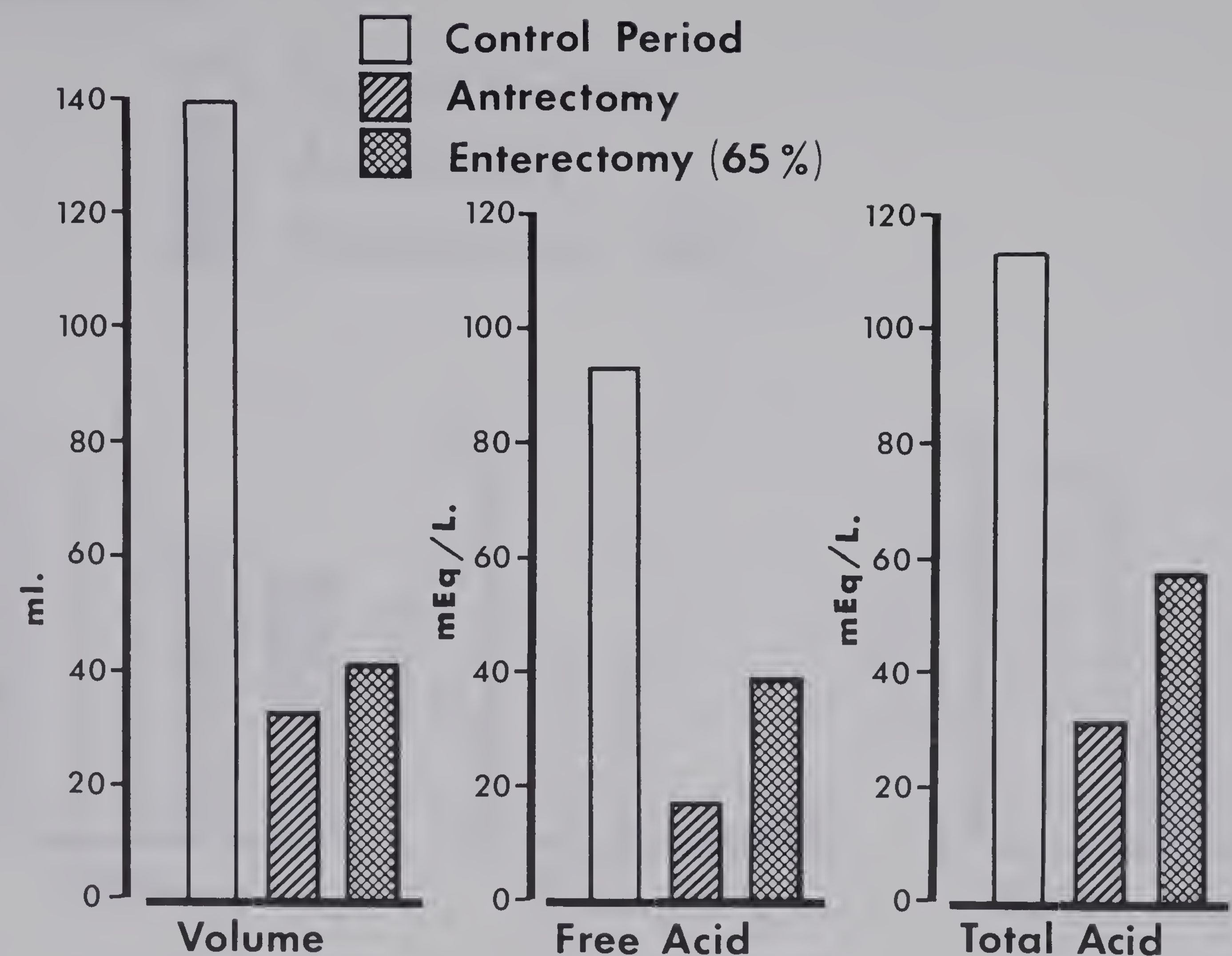


FIGURE 12. Comparison of the 24 hour post-prandial H.P. secretion of group B dogs. Antrectomy markedly decreased the mean volume, and free and total acids of the H.P. secretion. Enterectomy had no significant effect on the mean volume and free acid, but significantly increased the mean total acid of the H.P. secretion of antrectomised dogs.

Mean 24 Hour Fasting Heidenhain Pouch Secretion

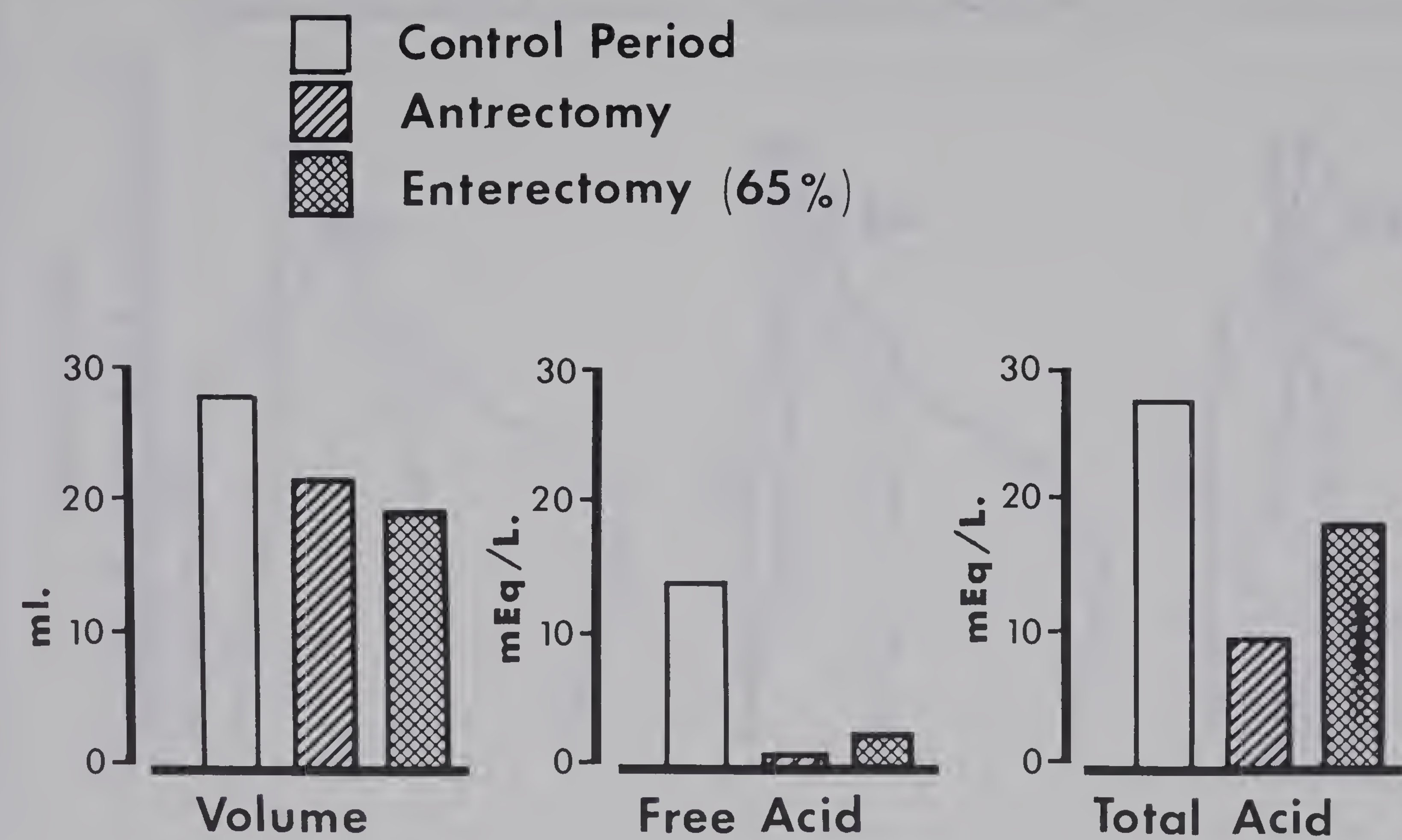


FIGURE 13. Comparison of the 24 hour fasting H.P. secretion of group B dogs. Antrectomy had no significant effect on the mean volume but markedly decreased the mean free and total acids of the H.P. secretion. Enterectomy had no significant effect on the mean volume, and free and total acids of the H.P. secretion of antrectomised dogs.

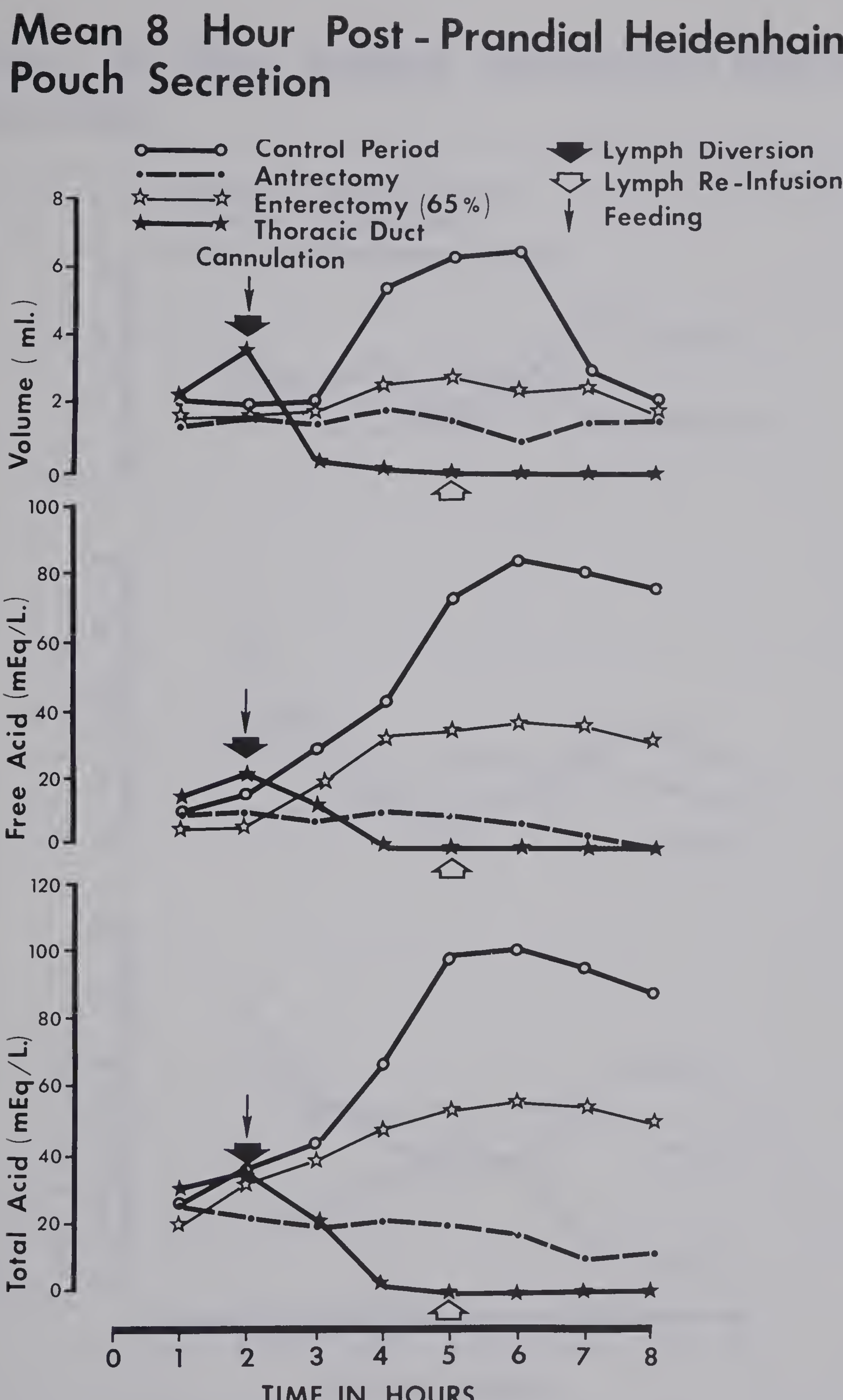


FIGURE 14. Comparison of the mean hourly H.P. secretion of group B dogs in the post-prandial period. Antrectomy markedly decreased the mean volume, and free and total acids of the H.P. secretion. Enterectomy significantly increased these parameters in the antrectomised dogs. Lymph diversion markedly decreased the mean volume, and free and total acids in the antrectomised and enterectomised dogs, whereas lymph reinfusion had no significant change in these parameters of the H.P. secretion in dogs with lymph diversion.

Mean 8 Hour Fasting Heidenhain Pouch Secretion

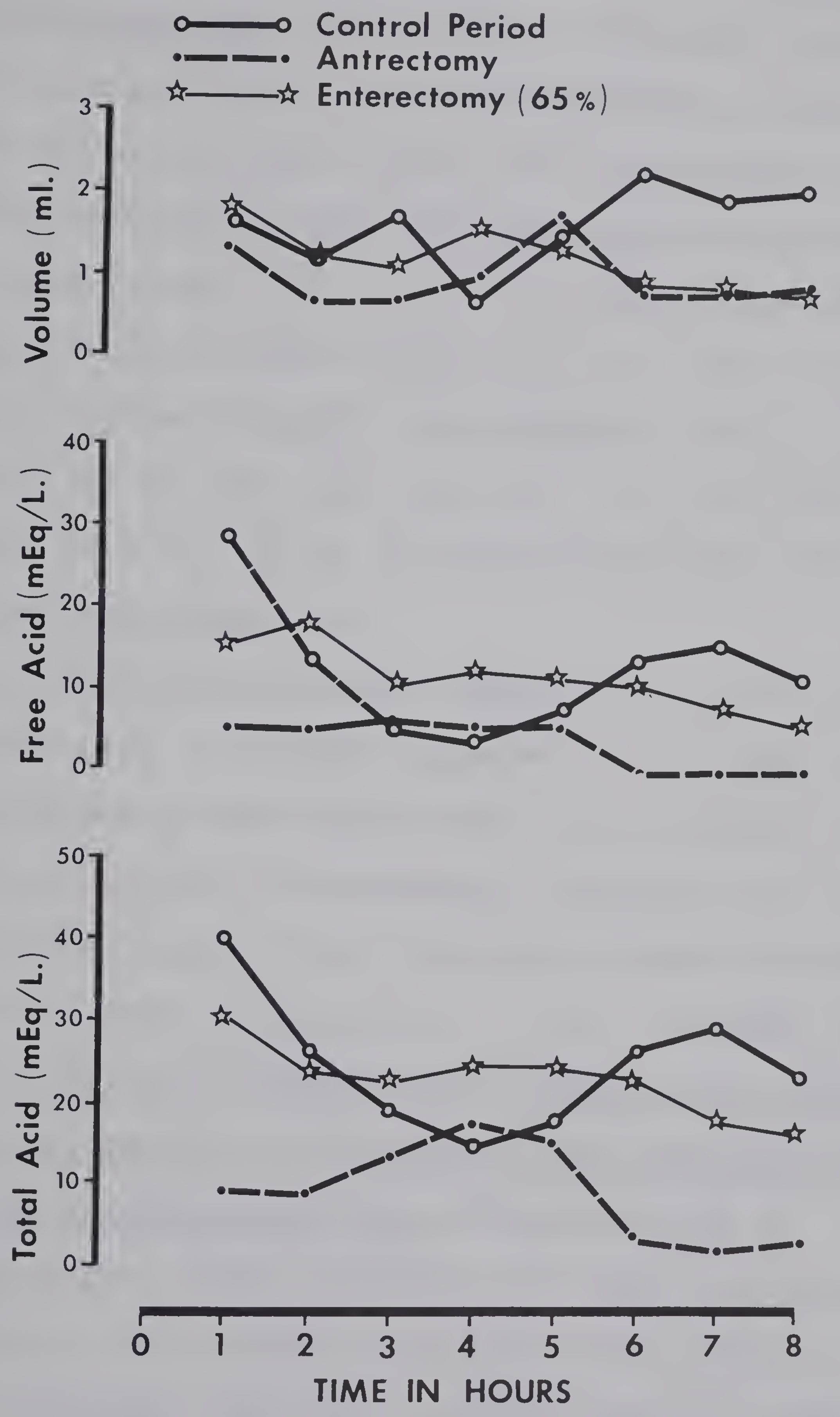


FIGURE 15. Comparison of the mean hourly H.P. secretion of group B dogs in the fasting period. Antrectomy had no significant effect on the mean volume, and free and total acids of the H.P. secretion. Enterectomy had no significant effect on the mean volume, but markedly increased the mean free and total acids of the H.P. secretion of the antrectomised dogs.

change as compared with the control (Figure 15).

B. Effect of Enterectomy on Heidenhain Pouch Secretion of Antrectomised Dogs (Table VIII). 65% small intestinal resection was performed in the hyposecreting, antrectomised dogs. After enterectomy, there was a significant increase in the 6-hour Heidenhain pouch secretion as shown by the 11.68% rise in mean volume (N.S.), 227.53% in mean free acid ($p < 0.01$) and 135.54% in mean total acid ($p < 0.01$) of the fasting secretion (Figure 15) and a 50% increase in mean volume ($p < 0.05$), 345.73% in mean free acid ($p < 0.01$) and 206.11% in mean total acid ($p < 0.01$) of the post-prandial Heidenhain pouch secretion (Figure 14).

In the 24-hour fasting secretion, a 16.96% decrease in mean volume (N.S.), 194.12% increase in free acid (N.S.) and 86.98% increase in mean total acid (N.S.) resulted (Figure 13).

In the 24-hour post-prandial secretion, an increase of 25.65% in mean volume (N.S.), 136.47% in mean free acid (N.S.) and 82.31% in mean total acid ($p < 0.05$) occurred (Figure 12).

C. Effect of Thoracic Duct Cannulation, Lymph Diversion and Lymph Reinfusion on Heidenhain Pouch Secretion of Antrectomised and Enterectomised Dogs (Tables IX and X). Thoracic duct cannulation, lymph diversion and lymph reinfusion were carried out in this group of animals as in Group A. When the lymph was diverted there was a sudden drop of 93.94% in mean volume ($p < 0.05$), 84.13% in mean free acid (N.S.) and 84.29% in mean total acid ($p < 0.05$) of the 3-hour Heidenhain pouch post-prandial secretion (Figure 14).

TABLE VIII

EFFECT OF ENTERECTOMY ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP B ANTRECTOMISED DOGS

	Antrectomy	Enterectomy	Difference %	P Value
24-Hour Fasting				
Volume*	23.00	19.10	-16.96	N.S.
Free Acid†	0.85	2.50	+194.12	N.S.
Total Acid†	9.60	17.95	+86.98	N.S.
24-Hour Post-Prandial				
Volume	32.70	41.15	+25.65	N.S.
Free Acid	16.45	38.90	+136.47	N.S.
Total Acid	31.65	57.70	+82.31	< 0.05
6-Hour Fasting				
Volume	5.91	6.6	+11.68	N.S.
Free Acid	17.80	58.3	+227.53	< 0.01
Total Acid	54.30	127.9	+135.54	< 0.01
6-Hour Post-Prandial				
Volume	9.20	13.8	+50.0	< 0.05
Free Acid	42.20	188.1	+345.73	< 0.01
Total Acid	98.20	300.6	+206.11	< 0.01

* Volume in ml.

† Acid in mEq./L.

TABLE IX

EFFECT OF LYMPH DIVERSION ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP B ANTRECTOMISED AND ENTERECTOMISED DOGS

	Enterectomy	Lymph Diversion	Difference %	P Value
3-Hour Post-Prandial				
Volume*	7.1	0.43	-93.94	< 0.05
Free Acid†	83.8	13.30	-84.13	N.S.
Total Acid†	141.1	22.17	-84.29	< 0.05

* Volume in ml.

† Acid in mEq./L.

TABLE X

EFFECT OF LYMPH REINFUSION ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP B DOGS WITH ANTRECTOMY, ENTERECTOMY AND LYMPH DIVERSION

	Lymph Diversion	Lymph Reinfusion	Difference %	P Value
3-Hour Post-Prandial				
Volume*	0.43	0.20	-53.48	N.S.
Free Acid†	13.30	0	-100.00	N.S.
Total Acid†	22.17	0	-100.00	N.S.

* Volume in ml.

† Acid in mEq./L.

During the reinfusion of lymph, the last three collections of the 6-hour post-prandial Heidenhain pouch secretion, the mean volume, free acid and total acid remained the same as before the reinfusion (Figure 14).

D. Effects of Sham Operations (Sham Enterectomy and Thoracotomy) on Heidenhain Pouch Secretion (Tables XI and XII). Four dogs in Group B underwent sham operations (sham enterectomy and thoracotomy). It was found that neither of these two sham operations had significant effect on the Heidenhain pouch secretion (Figures 16, 17, 18 and 19).

III. Heidenhain Pouch Secretion of Group C Dogs

A. Effect of 65% Small Intestinal Resection (Table XIII). As in Group A dogs, massive small intestinal resection in this group brought forth significant hypersecretion. The 24-hour post-prandial Heidenhain pouch secretion showed an increase of 124.75% in mean volume ($p < 0.05$), 207.5% in free acid ($p < 0.01$) and 98.01% in total acid ($p < 0.01$) (Figure 20). However, as in Group A, there was no significant change in the 24-hour fasting Heidenhain pouch secretion (Figure 21).

A similar increase of 193.75% in mean volume, 100% in mean free acid and 428.57% in mean total acid was also seen in the 6-hour fasting Heidenhain pouch secretion ($p < 0.01$) (Figure 22). In the 6-hour post-prandial Heidenhain pouch secretion, an increase of 144.44% ($p < 0.05$), 247.49% ($p < 0.01$) and 136.4% ($p < 0.01$) occurred in the mean volume, free acid and total acid respectively (Figure 23).

TABLE XI

EFFECT OF SHAM ENTERECTOMY ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP B ANTRECTOMISED DOGS

	Antrectomy	Sham Enterectomy	Difference %	P Value
24-Hour Fasting				
Volume*	15.0	15.0	0	N.S.
Free Acid†	0	0	0	N.S.
Total Acid†	3.5	1.5	-57.14	N.S.
24-Hour Post-Prandial				
Volume	28.2	27.2	-3.54	N.S.
Free Acid	11.0	13.0	+18.18	N.S.
Total Acid	28.0	29.0	+3.57	N.S.
6-Hour Fasting				
Volume	2.6	1.7	-32.55	N.S.
Free Acid	0	0	0	N.S.
Total Acid	22.9	19.9	-13.10	N.S.
6-Hour Post-Prandial				
Volume	3.9	4.4	+12.82	N.S.
Free Acid	0	0	0	N.S.
Total Acid	55.2	64.9	+15.57	N.S.

* Volume in ml.

† Acid in mEq./L.

TABLE XII

EFFECT OF THORACOTOMY ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP B ANTRECTOMISED AND ENTERECTOMISED DOGS

	Enterectomy	Thoracotomy	Difference %	P Value
6-Hour Post-Prandial				
Volume*	9.5	9.6	+1.05	N.S.
Free Acid†	227.6	206.1	-9.21	N.S.
Total Acid†	348.6	344.8	-1.09	N.S.

* Volume in ml.

† Acid in mEq./L.

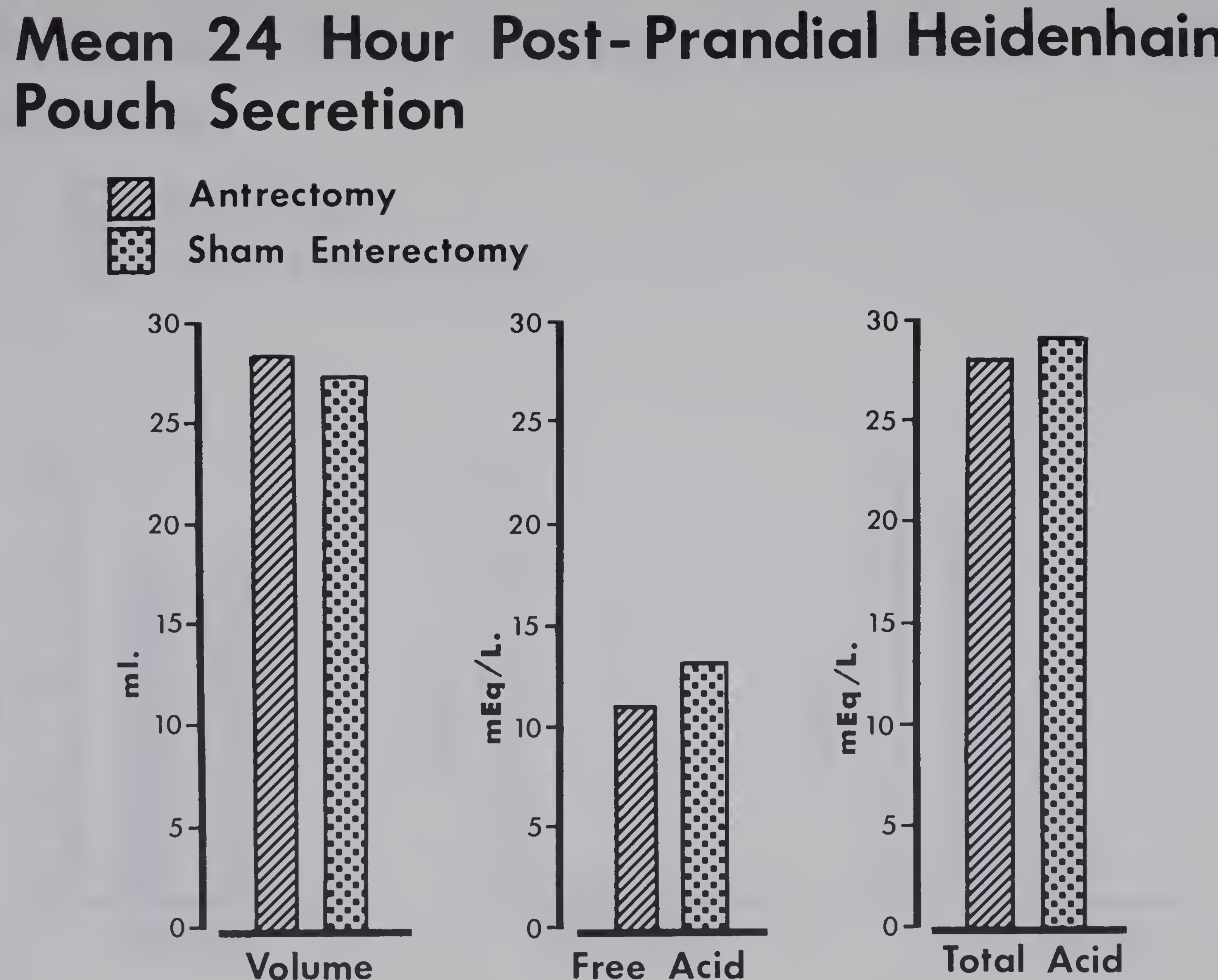


FIGURE 16. Effect of sham enterectomy on the mean 24 hour post-prandial H.P. secretion of group B dogs. Sham enterectomy had no significant effect on the mean volume, and free and total acids of the H.P. secretion in antrectomised dogs.

Mean 24 Hour Fasting Heidenhain Pouch Secretion

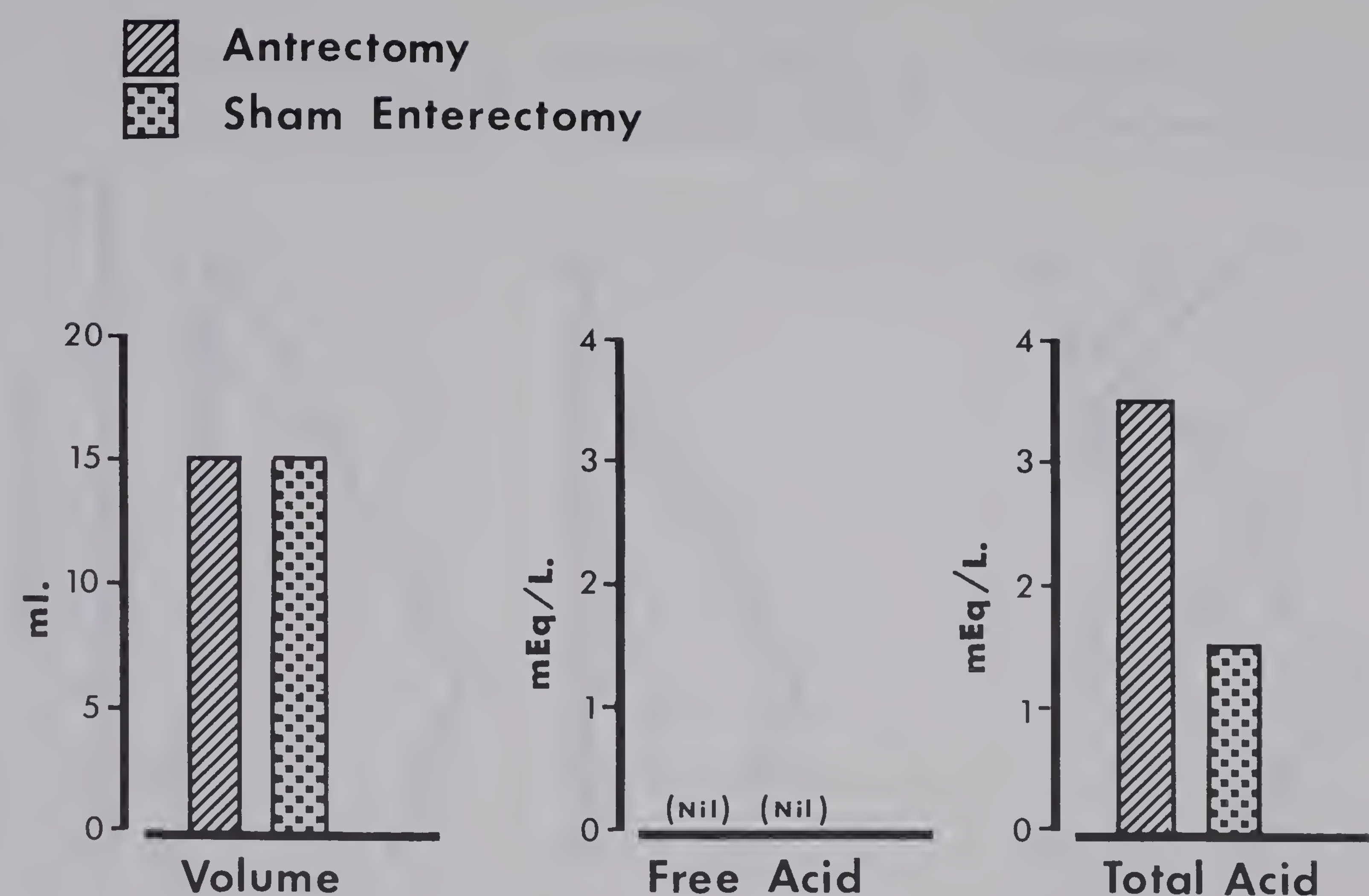


FIGURE 17. Effect of sham enterectomy on the mean 24 hour fasting H.P. secretion of group B dogs. Sham enterectomy had no significant effect on the mean volume, and free and total acids of the H.P. secretion in the antrectomised dogs.

Mean 8 Hour Post - Prandial Heidenhain Pouch Secretion

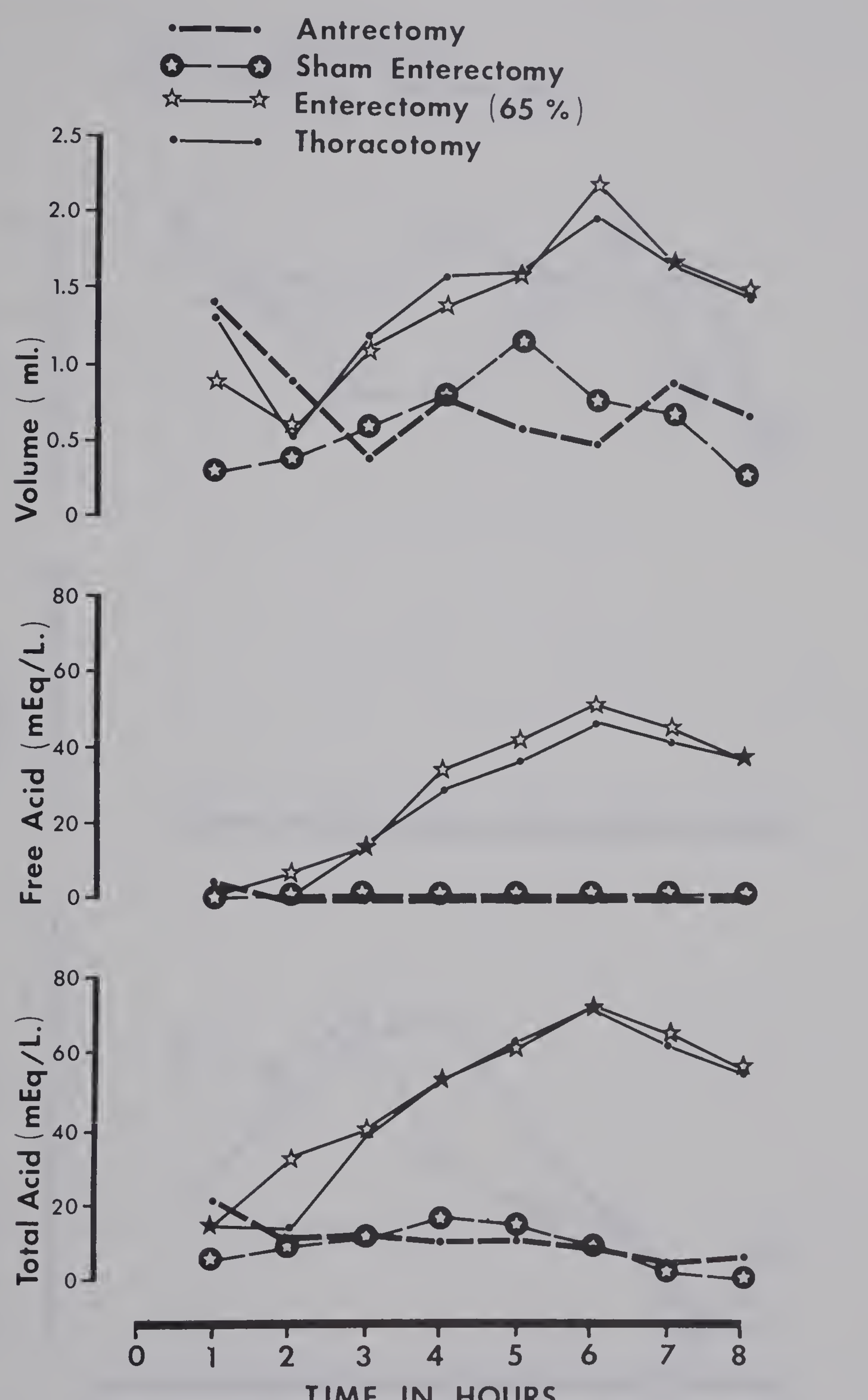


FIGURE 18. Effect of sham operation (sham enterectomy and thoracotomy) on the mean hourly volumes, and free and total acids of the post-prandial H.P. secretion of group B dogs. Sham enterectomy had no significant effect on the H.P. secretion of antrectomised dogs. Thoracotomy had no significant effect on the H.P. secretion in antrectomised and enterectomised dogs. Similar changes were observed in the mean free and total acids.

Mean 8 Hour Fasting Heidenhain Pouch Secretion

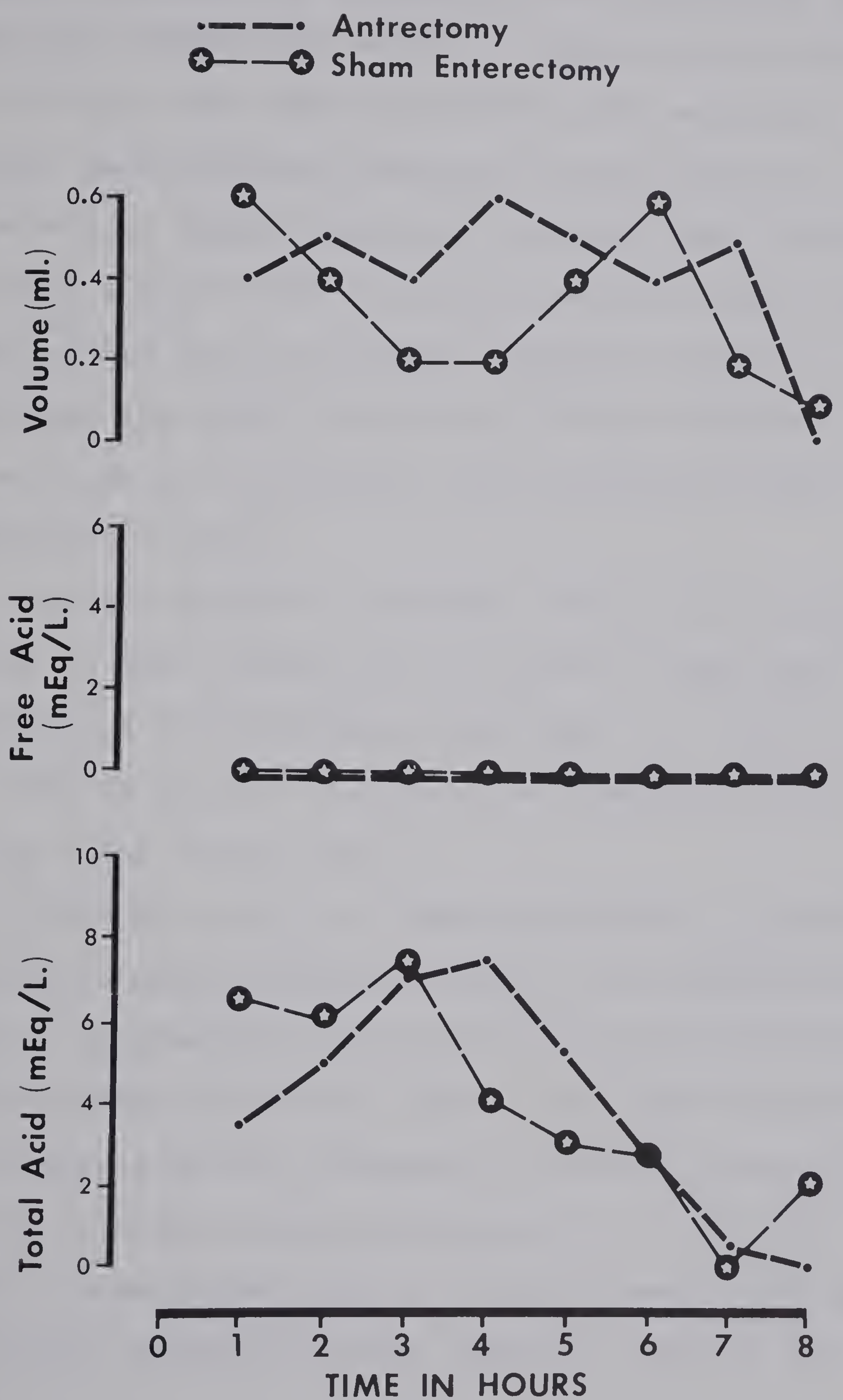


FIGURE 19. Effect of sham enterectomy on the mean hourly H.P. secretion of group B dogs in the fasting period. Sham enterectomy had no significant effect on the mean volume, and free and total acids of the H.P. secretion in the antrectomised dogs.

B. Effect of Thoracic Duct Cannulation, Lymph Diversion and Lymph Reinfusion on Heidenhain Pouch Secretion of Enterectomised Dogs (Tables XIV and XV). Thoracic duct cannulation, lymph diversion and lymph reinfusion were performed during the 6-hour post-prandial Heidenhain pouch secretion in these hypersecreting, small intestinal resected dogs. During the first three hours of the collection period, lymph diversion was carried out and the diverted lymph was collected. Immediately after the third collection, all the diverted lymph was reinfused back to the animals over a period of three hours via the intravenous route.

When the lymph was diverted, there was an abrupt drop of 87.22% in mean volume (N.S.), 98.43% in mean free acid ($p < 0.05$) and 92.9% in mean total acid ($p < 0.05$) of the 3-hour Heidenhain pouch secretion as compared with the hypersecreting state (Figure 23).

During the period of lymph reinfusion, a marked rise of Heidenhain pouch secretion back to its hypersecreting state resulted. On comparing this period of pouch secretion with the first three collections, where only lymph diversion was taking place, a 791.3% increase in the mean volume ($p < 0.01$), 4,625.71% increase in mean free acid ($p < 0.05$) and 1,136.32% increase in mean total acid ($p < 0.05$) occurred in the hourly post-prandial Heidenhain pouch secretion (Figure 23).

TABLE XIII

EFFECT OF ENTERECTOMY ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP C DOGS

	Control	Enterectomy	Difference %	P Value
24-Hour Fasting				
Volume*	15.62	21.87	+40.00	N.S.
Free Acid†	0	0	0	N.S.
Total Acid†	3.25	14.87	+357.69	N.S.
24-Hour Post-Prandial				
Volume	24.75	55.62	+124.75	<0.05
Free Acid	25.00	76.80	+207.50	<0.01
Total Acid	50.25	99.50	+98.01	<0.01
6-Hour Fasting				
Volume	1.6	4.7	+193.75	<0.01
Free Acid	0	130.1	-	<0.01
Total Acid	46.2	244.2	+428.57	<0.01
6-Hour Post-Prandial				
Volume	8.1	19.80	+144.44	<0.05
Free Acid	147.6	512.90	+247.49	<0.01
Total Acid	258.8	611.86	+136.40	<0.01

* Volume in ml.

† Acid in mEq./L.

TABLE XIV

EFFECT OF LYMPH DIVERSION ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP C ENTERECTOMISED DOGS

	Enterectomy	Lymph Diversion	Difference %	P Value
3-Hour Post-Prandial				
Volume*	7.2	0.92	-87.22	N.S.
Free Acid†	222.7	3.50	-98.43	< 0.05
Total Acid†	282.9	20.10	-92.90	< 0.05

* Volume in ml.

† Acid in mEq./L.

TABLE XV

EFFECT OF LYMPH REINFUSION ON MEAN HEIDENHAIN POUCH SECRETION OF GROUP C DOGS WITH ENTERECTOMY AND LYMPH DIVERSION

	Lymph Diversion	Lymph Reinfusion	Difference %	P Value
3-Hour Post-Prandial				
Volume*	0.92	8.2	+791.30	< 0.01
Free Acid†	3.50	165.4	+4625.71	< 0.05
Total Acid†	20.10	248.5	+1136.32	< 0.05

* Volume in ml.

† Acid in mEq./L.

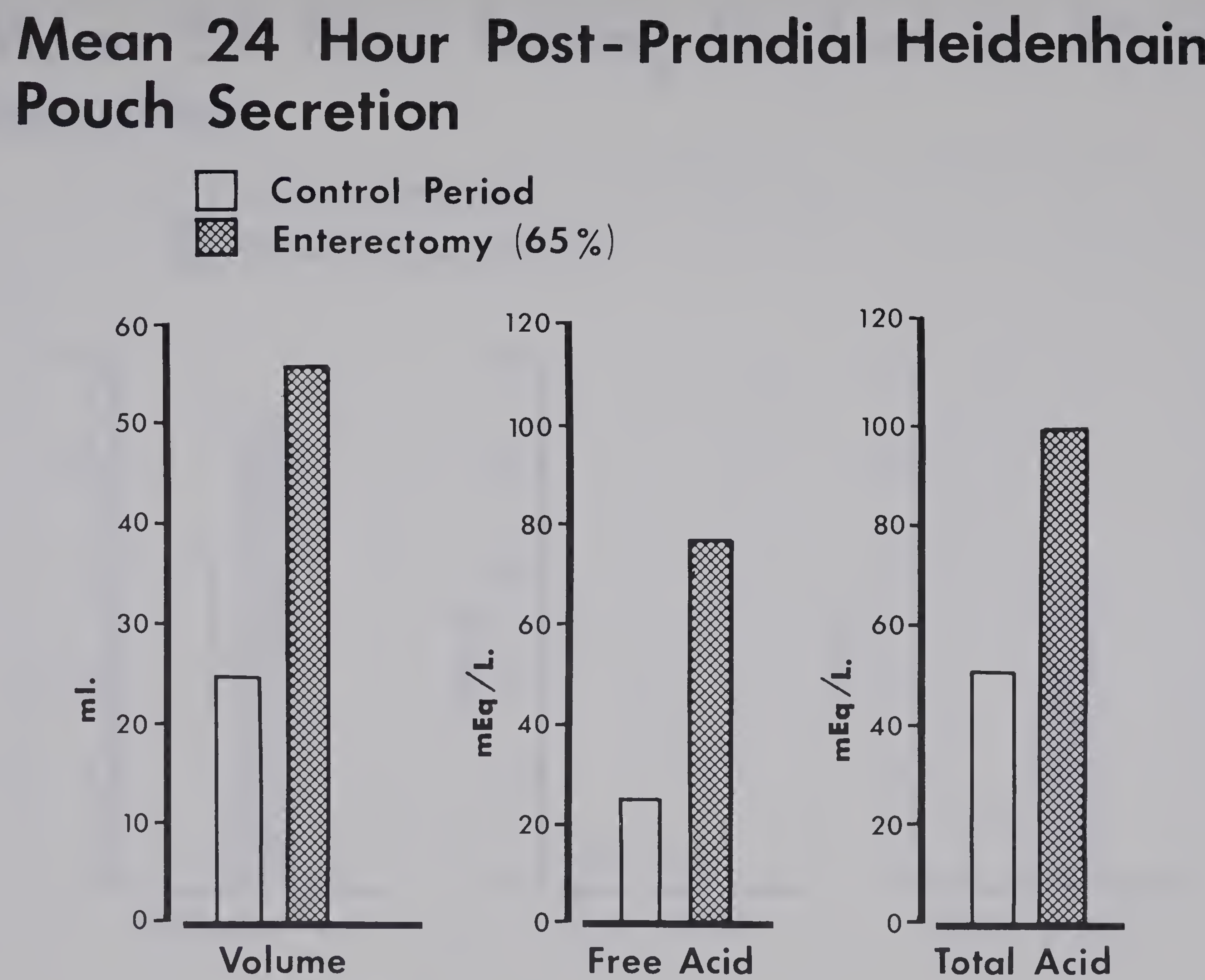


FIGURE 20. Effect of enterectomy on the mean 24 hour post-prandial H.P. secretion of group C dogs. Enterectomy markedly increased the mean volume, and free and total acids of the H.P. secretion.

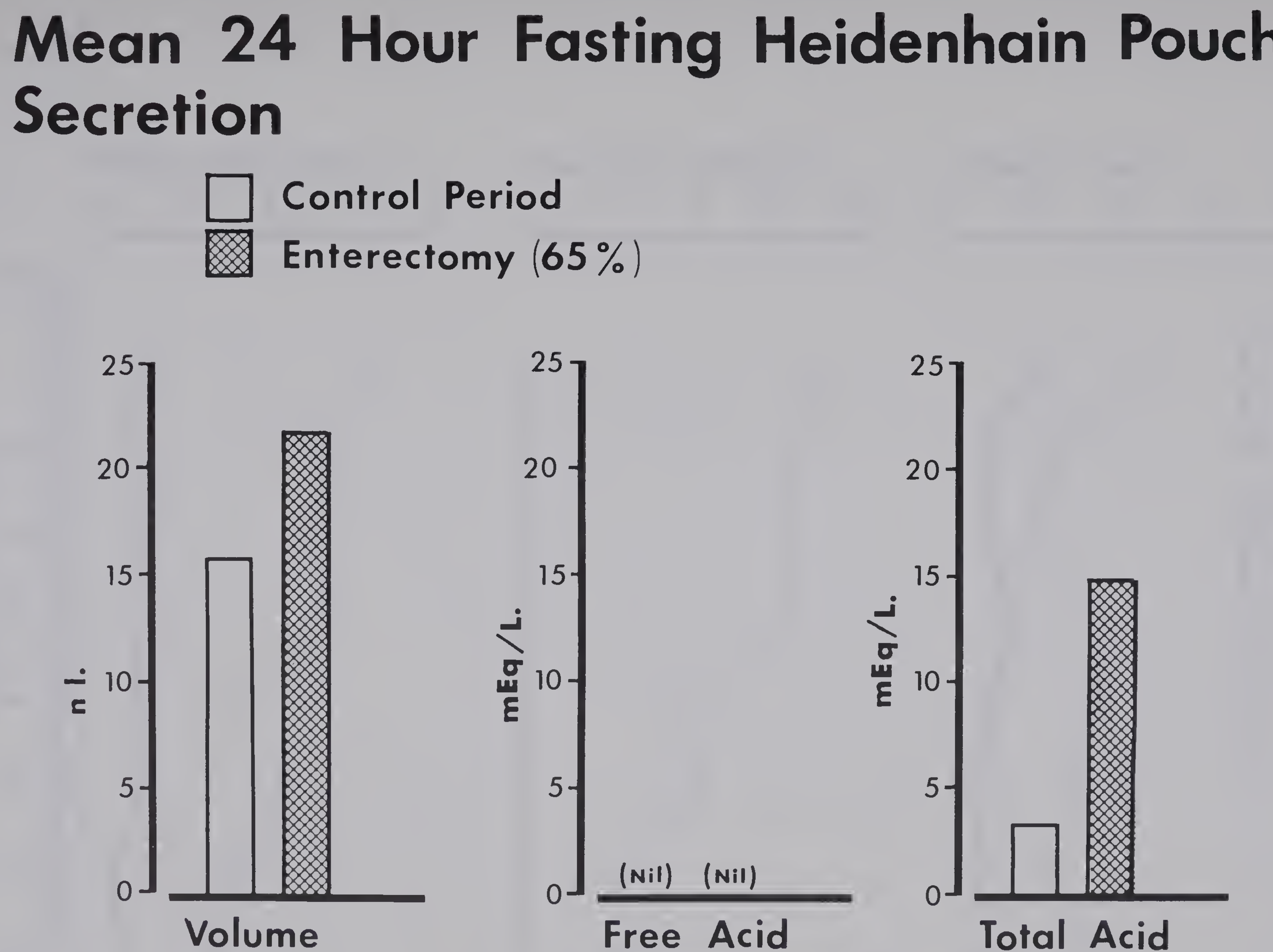


FIGURE 21. Effect of enterectomy of the mean 24 hour fasting H.P. secretion of group C dogs. Enterectomy had no significant effect on the mean volume, and free and total acids of the H.P. secretion.

Mean 8 Hour Fasting Heidenhain Pouch Secretion

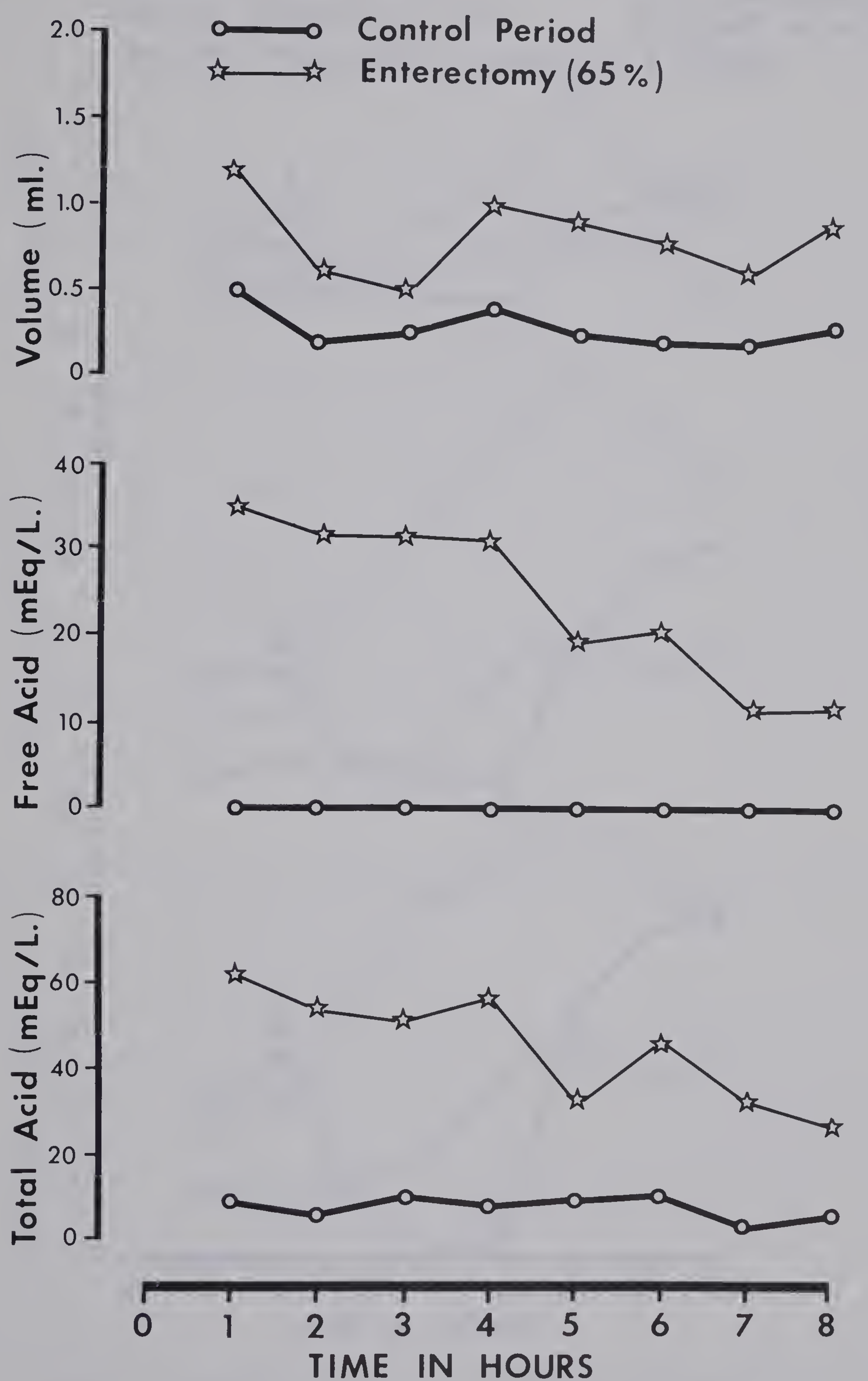


FIGURE 22. Effect of enterectomy on the mean hourly fasting H.P. secretion of group C dogs. Enterectomy markedly increased the mean volume, and free and total acids of the H.P. secretion.

Mean 8 Hour Post-Prandial Heidenhain Pouch Secretion

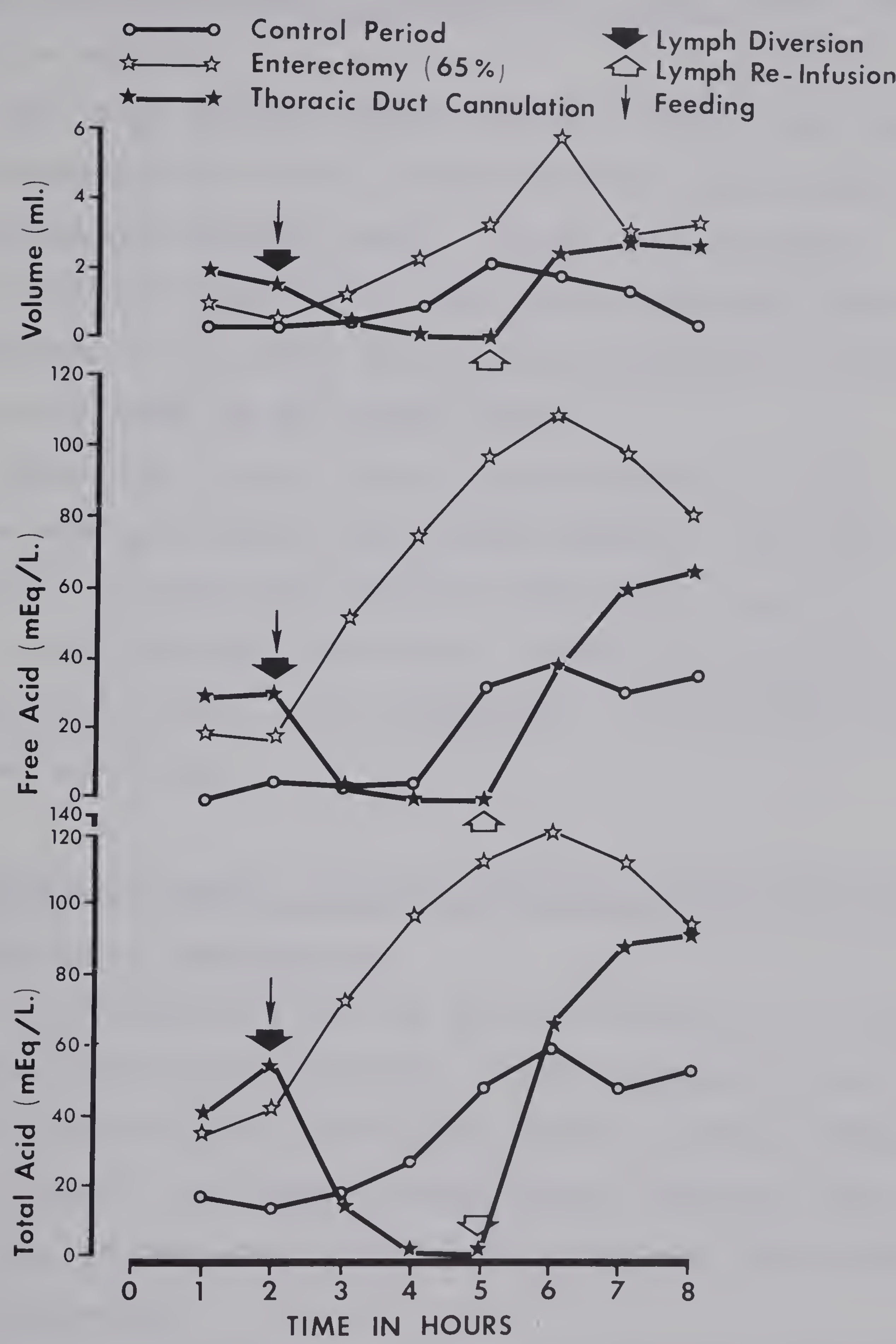


FIGURE 23. Comparison of the mean hourly H.P. secretion of group C dogs in the post-prandial period. Enterectomy markedly increased the mean volume, and free and total acids. Lymph diversion had no significant effect on the mean volume, but markedly decreased the mean free and total acids of the H.P. secretion of enterectomised dogs. Reinfusion of diverted lymph significantly increased the mean volume, and free and total acids.

IV. Effect of 65% Small Intestinal Resection on Liver Function Studies, Liver Histology and Hemoglobin in Dogs (Table XVI, Figures 24 and 25)

The liver function tests that were used in this study were Bromsulphalein (B.S.P.) retention test, serum total protein and albumin-globulin ratio. As the data of normal albumin-globulin ratio varies widely with individual dogs, the findings of this ratio in the control period of the experiment were taken as the normal value.

Hemoglobin levels, liver function tests and liver biopsies were performed in the control period. They were repeated 4 - 6 weeks after massive small bowel resection.

It was observed that massive intestinal resection had no significant effect on the hemoglobin, liver function tests and liver histology.

V. Barium Meal Studies on Gastric Emptying Time in Pre- and Post-Intestinal Resected Dogs

Gastric emptying time of dogs was studied by the use of radiological barium meal studies. Complete emptying was considered to have occurred when only traces of barium remained in the stomach. The normal average gastric emptying time of barium meal of dogs with a Heidenhain pouch was about three hours (Figure 26).

Barium meal studies were repeated after 65% resection of small intestine. It was noted that enterectomy had no detectable effect on barium meal gastric emptying time (Figure 27).

TABLE XVI

EFFECT OF ENTERECTOMY ON MEAN LIVER FUNCTION TESTS AND MEAN HEMOGLOBIN LEVEL OF GROUP A DOGS

	Control	Enterectomy	Difference %	P Value
B.S.P.*	3.3	3.48	+5.45	N.S.
Total Protein†	6.42	6.37	-0.77	N.S.
Albumin-Globulin	0.87/1	0.92/1	+5.74	N.S.
Hemoglobin+	13.48	13.35	-0.96	N.S.

* B.S.P. in percentage of retention

† Total protein in gm. per 100 ml.

\+ Hemoglobin in gm. per 100 ml.

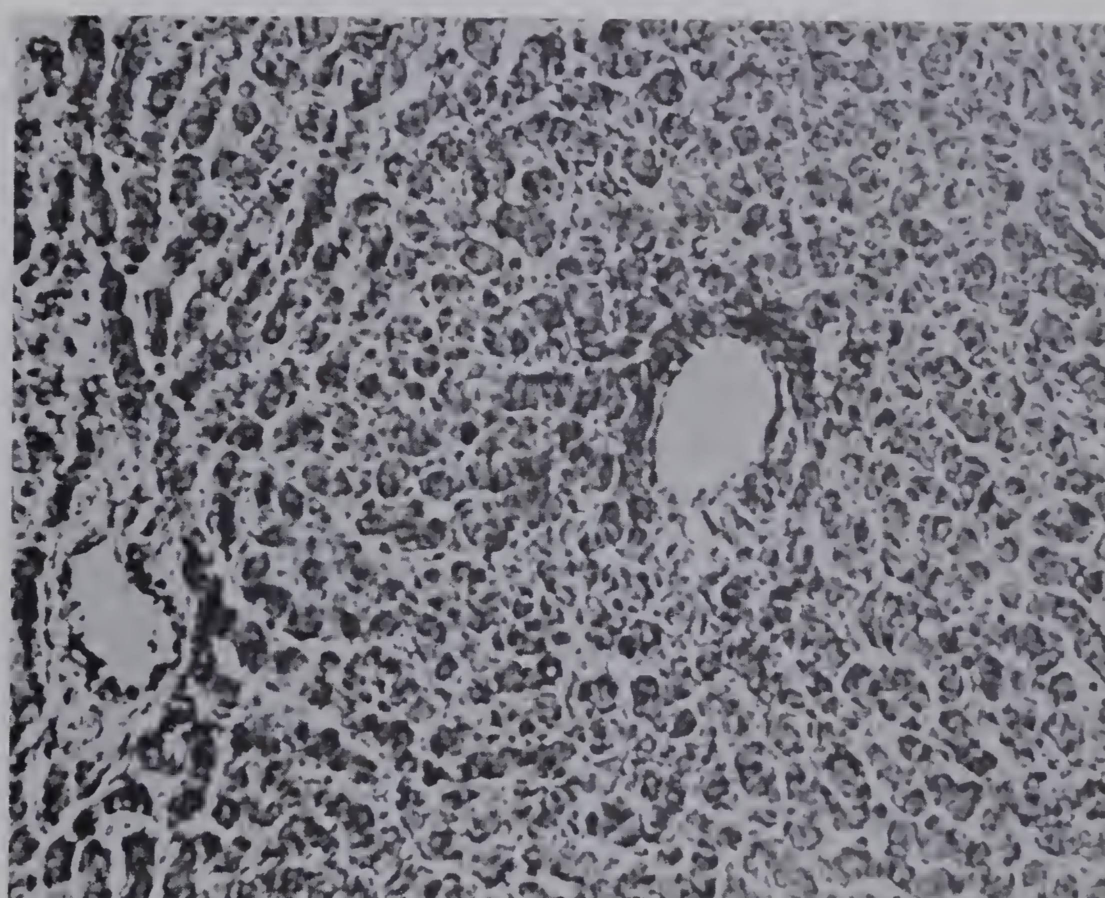


FIGURE 24. LIVER BIOPSY OF DOG NO. 1125 IN THE CONTROL PERIOD. NORMAL. X 100 (SUDAN IV STAIN).

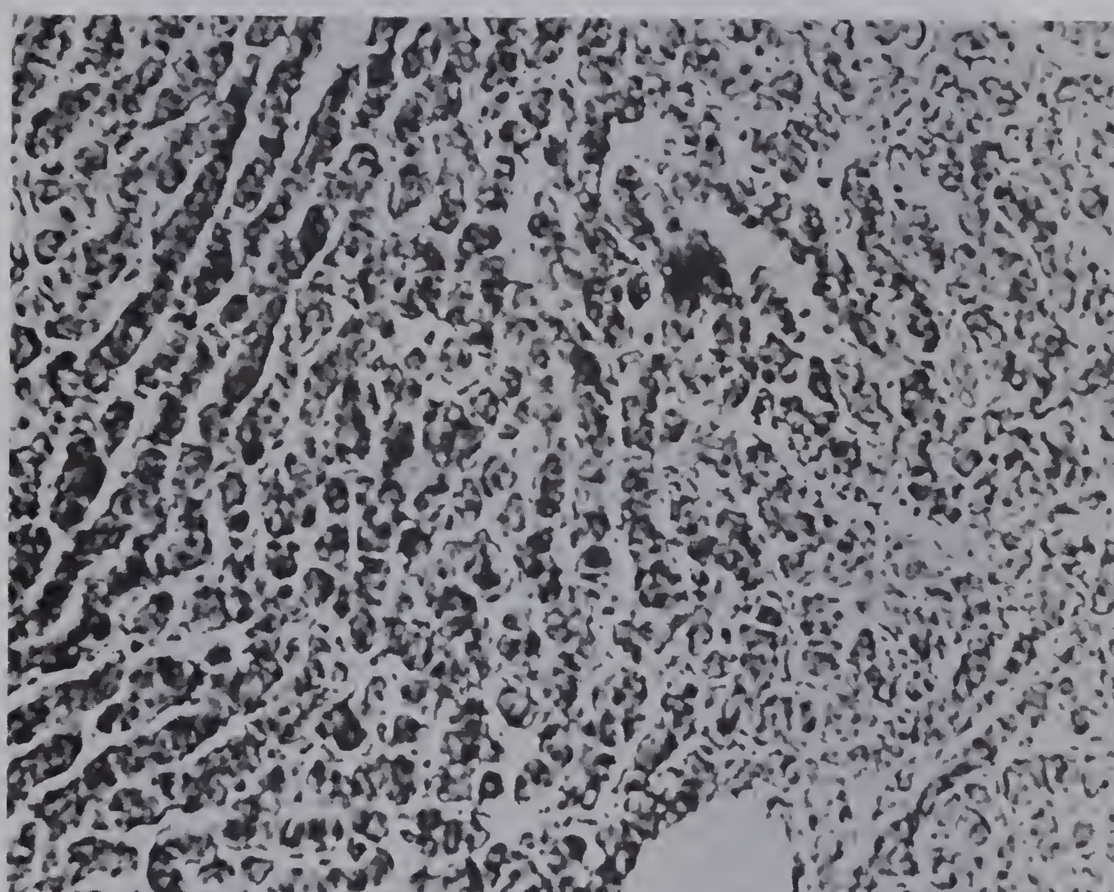
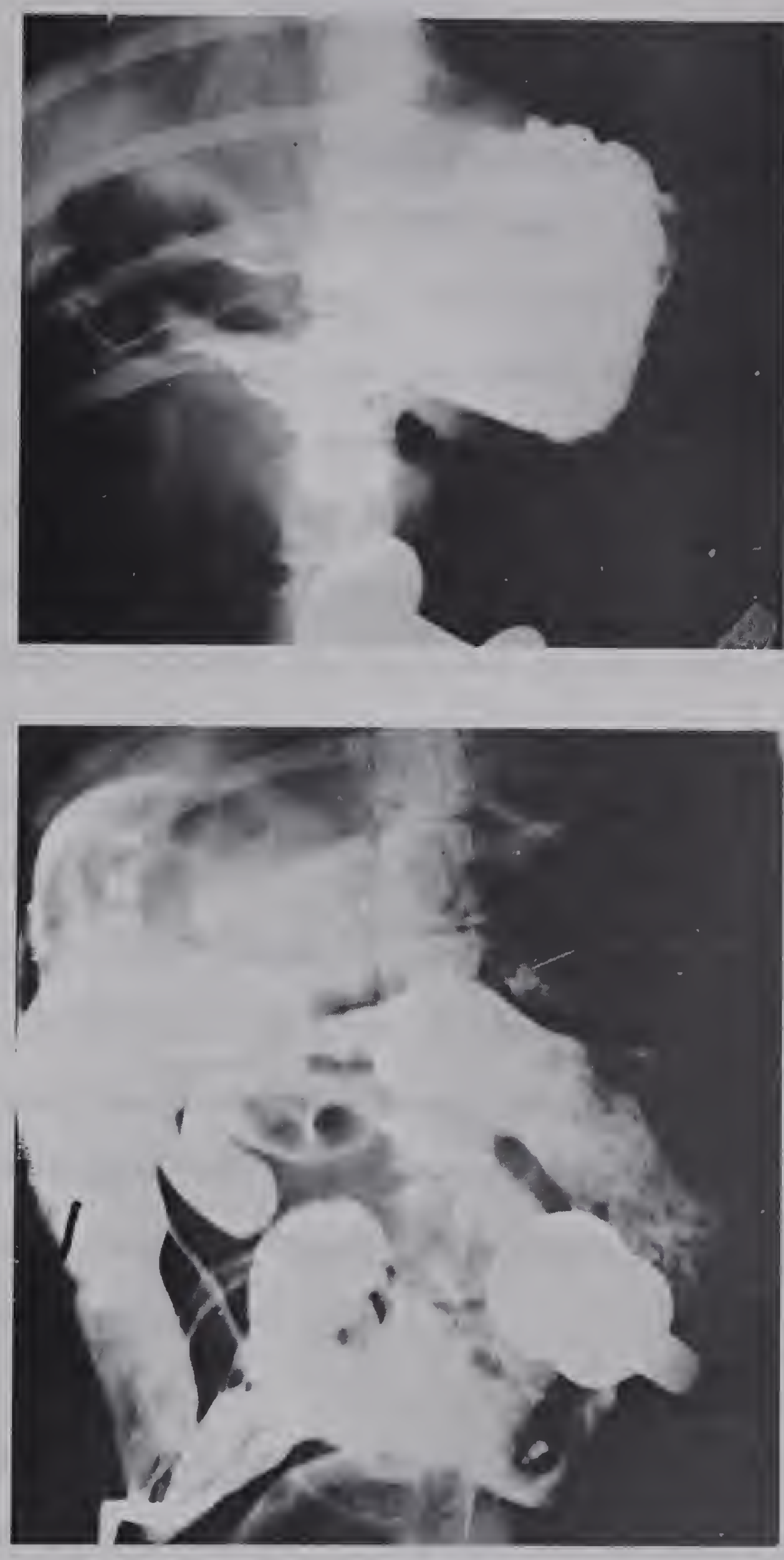


FIGURE 25. LIVER BIOPSY OF DOG NO. 1125 AT 6 WEEKS AFTER ENTERECTOMY. NO SIGNIFICANT CHANGE AS COMPARED WITH THE CONTROL PERIOD. X 100 (SUDAN IV STAIN).

(A)

(B)

FIGURE 26. BARIUM MEAL GASTRIC EMPTYING STUDY IN THE CONTROL PERIOD OF DOG NO 1284: (A) X-RAY PICTURE TAKEN IMMEDIATELY AFTER BARIUM MEAL WAS SWALLOWED. (B) X-RAY PICTURE TAKEN 3 HOURS LATER SHOWED COMPLETE EMPTYING OF THE STOMACH.



(A)

(B)

FIGURE 27. BARIUM MEAL GASTRIC EMPTYING STUDY IN THE POST-ENTERECTOMY PERIOD OF DOG NO. 1284: (A) X-RAY PICTURE TAKEN IMMEDIATELY AFTER THE BARIUM WAS SWALLOWED. (B) X-RAY PICTURE TAKEN 3 HOURS LATER SHOWED COMPLETE EMPTYING OF THE STOMACH.

DISCUSSION

The findings of this study clearly demonstrate that after an extensive resection of the small intestine, a sharp rise of Heidenhain pouch secretion occurs, and that antrectomy before or after enterectomy can markedly reduce this hypersecretion. Though antrectomy can prevent gastric hypersecretion after small intestinal resection, it is interesting to note that small intestinal resection in an antrectomised dog can still bring forth a higher Heidenhain pouch secretion than in the animal with only an antrectomy (Group B dogs, Table VIII). It is upon this observation that our hypothesis on the mechanism of gastric hypersecretion following massive small intestinal resection will be based.

Certain factors involving stimulation or decreased inhibition of the gastric acid secretion are most likely to play an important part in the mechanism of gastric hypersecretion following massive small intestinal resection. These factors are discussed below.

I. Consideration of the Loss of Inhibitors

A number of substances secreted by or into the gastrointestinal tract have been demonstrated to have inhibitory effects on gastric secretion. These substances include gastrone, enterogastrone, secretin, serotonin, cholecystokinin, bile, histaminase and other unidentified chalones.

A. <u>Gastrone and Chalone</u>. Brunschwig and associates

(14, 15) were the first to demonstrate that human gastric juice contains a substance capable of inhibiting gastric acid secretion. They called this inhibitory substance 'gastrone'. This was later proved by others (59), who also found that the same substance, or a substance of similar action, was present in human saliva.

Menguy et al. (88) have shown that a certain acid inhibitor is derived from the antral mucous, while Harrison et al. (56) and Thompson et al. (120) have extensively studied a possible antral chalone. When a large portion of the small intestine has been resected, the loss of absorption of such inhibitory factors could represent the mechanism producing hypersecretion. If loss of these antral gastric inhibitors played an important part in producing hypersecretion, antrectomy should lead to further hypersecretion, but it was not so in our experimental findings. Our dogs with intestinal resection (Group A) stopped hypersecreting after antrectomy. This suggests that probably the presence of an antral gastric secretory hormone, gastrin or others, has greater influence than the loss of antral chalone in regulating hypersecretion.

B. Enterogastrone. Enterogastrone has been considered an inhibitor of gastric secretion. Ever since it was first described by Kosaka and Lim (73) in 1930, its existence has been increasingly questioned (39). It is generally thought to be released by the presence of fat in the upper small intestine. However, we are uncertain that fat plays a significant role in the regulation of the twenty-four hour gastric secre-

tion, particularly when it has been shown that fat does not affect the total output of acid and pepsin in response to food though they can delay the peak gastric secretion.

C. Secretin and Cholecystokinin. Both secretin and cholecystokinin are released from the upper intestine. Besides their respective actions on the pancreas and gall bladder, they have been discovered to have inhibitory action on gastric secretion (35, 38, 71). In our experimental animals, we only resected the small intestine from a point two feet distal to the ligament of Treitz to a point one foot proximal to the ileocecal valve, which means that the duodenum and upper two feet of jejunum were intact. With this portion of upper small intestine undisturbed, the secretion of secretin and cholecystokinin should then not be affected. Yet gastric hypersecretion still occurred in our resected animals. In addition, Osborne et al. (96) demonstrated that the lower, rather than the upper, small intestinal resection resulted in a greater rise in secretion.

D. Serotonin. It has also been shown that serotonin has an inhibitory effect on gastric secretion (12, 57, 106, 107) and that it exists throughout the small intestine in measurable quantities (28). Serotonin release from intestinal mucosa has been observed after contact with acid (102), and with hypertonic solution (28, 95). Although a definite role for endogenous serotonin in regulating gastric function has yet to be explored, it is conceivable that serotonin is liberated during the passage of chyme through the small intestine, and that it possibly acts as an inhibitor of gastric secretion. After

massive small intestinal resection, there may be a quantitative reduction in the amount of serotonin available for pick-up by the portal and lymphatic circulation (75).

Yakimets and Bondar (134) suggested that thoracic duct lymph played an important role in regulating gastric secretion by transporting gastric secretogogues and inhibitors, and bypassing the detoxifying powers of the liver. In this case, diversion of thoracic duct lymph may remove the serotonin and induce hypersecretion, but our results showed that there was a marked decrease in pouch secretion when lymph diversion by supradiaphragmatic thoracic duct cannulation was performed.

E. Bile. Diversion of bile from the intestinal tract has been shown to bring forth gastric hypersecretion and peptic ulceration (85, 89). Nicoloff (92) explained that this was due to loss of bile salts which are believed to have inhibitory effects when administered intravenously. After massive small intestinal resection, the bile salts may be lost because of inadequate absorptive surface, thus possibly causing gastric hypersecretion.

F. Histaminase. While histaminase is found throughout the gastro-intestinal tract except for the stomach (17), it is observed that gastric secretion decreases when exogenous histaminase is administered to dogs (51), and that histaminase inhibitors augment various secretory responses (109). In dogs after massive intestinal resection, secretion of histaminase may be inadequate owing to removal of secretory surface. Loss of its inhibition of histamine at the parietal cell level could

help to produce hypersecretion. However, there is no proof for the role of this substance, and antihistaminic drugs, unless applied directly to the mucosa, have no effect at all on the parietal cell acid secretion (13).

Although in this study there was no evidence that the gastric hypersecretion following massive small intestinal resection is due to the loss of gastric inhibitor(s), the author cannot absolutely deny the possibility of such an occurrence. It it does occur, the loss of the inhibitory effect is likely to be at the antral gastrin level with this gastric secretory hormone unopposed, rather than at the parietal cells directly. This hypothesis is supported by the findings that the acid output of the small intestinal resected dogs had a sharp decrease well below the normal level after antrectomy was performed (Table III).

II. Consideration of the Gain of Secretogogue(s)

A. Gastric Retention. Antral retention is known to cause gastric hypersecretion, apparently because of prolonged antral stimulation and resulting gastrin release (52). Stahlgren et al. (114) proposed that after massive intestinal resection there was prolonged gastric emptying time and consequent antral distension with increased gastrin release, thus causing gastric hypersecretion. This proposal has been disputed by others (75, 96). The author measured gastric emptying time before and after intestinal resection by radiological barium meal studies, and found that the experimental animals showed no

gastric stasis after the intestinal resection, therefore making excessive antral effect due to delayed emptying unlikely.

B. Impairment of Liver Function. The impairment of liver function to inactivate secretogogues following enterectomy is believed by some to be an important factor (108). Many other workers (75, 96) including the author could find no abnormalities in liver function tests, nor any abnormal liver histology that could explain the rise of acid secretion in the bowel resected animals. In addition, the onset of hypersecretion was immediate in the resected animals, whereas changes in secretion due to progressive liver damage would be expected to be more gradual.

C. Infection. Howe (60) implicated wound infection as a cause for increased pouch secretion, but this factor was not noted in our animals.

D. Corticosteroids. Corticosteroids have been shown to increase gastric secretion in man (37). It has been suggested that adrenalin steroid levels in blood and urine are increased in the post-operative period (91) and thus cause hypersecretion. This has been disputed by many other workers (30, 96). In our experimental animals, the sham operations did not have any significant effect on the acid output from Heidenhain pouches. If there were increased serum corticosteroid levels in the post-operative period, the sham operations should also raise the corticosteroid levels and cause an increase in acid output.

E. Secretogogue(s) from Retained Intestine. Diversion of bile and pancreatic juice from the duodenum is known to bring about acid secretion (36, 87). Though it is not too

pertinent here, shortening of the small intestine by extensive resection can make possible the rapid passage of duodenal contents into the terminal ileum and colon. This rapid passage of duodenal contents of bile, pancreatic juice and improperly digested food into the terminal ileum and colon may not only alter the pH, but also stimulate this part of the intestine chemically by the partially digested protein, carbohydrate and fat, and physically by the abnormal distension of the intestine.

These factors may call in normal physiological responses to correct the change of pH, and to restore proper digestion of food by stimulating the release of gastric secretogogue(s) from the retained intestine, large and small. It has been shown that introduction of food into the duodenum and jejunum (66) or distension (110) of this section of intestine excites gastric secretion. Though the author is not aware of similar experiments in the ileum and colon, this may cause similar effect in this unusual situation of massive small intestinal resection.

The hypothesis of the secretion of a gastric secretogogue(s) from the remaining intestine after an extensive small intestinal resection is supported by findings in our animals (Group B) which showed that after enterectomy in the antrectomised dogs, there was a significant increase in Heidenhain pouch acid output. The origin of this gastric secretogogue(s) cannot be the antrum as all the animals have complete antrectomy (confirmed by histological examination). It may be from the retained small or large intestine. Lai (74) in 1964 extracted gastrin material from the duodenum of hogs. Similar hormone(s)

may also be present in the rest of the small intestine.

Though there was significant increase in acid output after enterectomy in antrectomised dogs, this acid level is still much lower than the control period (Figures 12 and 14). Also, antrectomy was associated with a reduction of acid output to a lower level in the hypersecreting intestinal resected animals (Group A). It seems, therefore, that an antral factor, probably gastrin, is involved as the immediate stimulus. The secretogogue(s) from the retained intestine is perhaps itself a weak gastric stimulator, which may act to potentiate and/or stimulate the antral gastrin mechanism in producing gastric hypersecretion following resection of the small intestine.

This second hypothesis is supported by the findings of the effect of diverson and reinfusion of thoracic duct lymph in our experimental animals.

Yakimets and Bondar (134) have shown that thoracic duct lymph plays an important role in regulating gastric secretion by carrying some gastric secretogogue(s) and perhaps bypassing the detoxifying powers of the liver. They also demonstrated that with diversion of thoracic duct lymph in the hypersecreting, intestinal resected dogs, a sharp drop of Heidenhain pouch secretion occurs, and on reinfusion of the diverted lymph into the animals, the acid output returns to the hypersecreting state. The findings in our experimental animals (Group C) agreed with their observation (Tables XIV and XV, Figure 23). Effect of the possible allergic response of the experimental dogs during the period of lymph infusion has been ruled out by the negative

findings of careful observations for excessive salivation, chills and rigors, or change of rectal temperature. It thus indicated that a gastric secretogogue is present in the thoracic duct lymph. This gastric secretogogue is probably antral gastrin, as all these animals have intact antral function.

The same experiment of lymph diversion and refinusion was performed in our Group A and Group B dogs, i.e., animals with massive small intestinal resection and antrectomy. Though there was marked decrease of Heidenhain pouch secretion when the lymph was diverted, no return of increased acid output occurred when the diverted lymph was reinfused back to the animals. The marked drop of pouch secretion on lymph diversion indicates a loss of secretogogue(s) through the diverted lymph. This secretogogue(s) cannot be antral gastrin because all the animals have antrectomy. It is likely to come from the retained small or large intestine as pointed out above.

Theoretically, when the diverted lymph was reinfused back to the dogs, there should be a return of Heidenhain pouch secretion to the level of pre-thoracic duct lymph diversion as occurred in Group C dogs (dogs with intact antral function). On the contrary, Heidenhain pouch secretion of these animals (dogs with antrectomy, Groups A and B) remains on the same low level as before lymph reinfusion. Three possible explanations can be given for this. Firstly, the heparin which was added to prevent clotting of the diverted lymph may have inhibitory effect on gastric secretion (119). However, the dose of heparin used was so small (5 mg. per 100 cc. of lymph) that its effect on gastric

secretion could be neglected (105). Secondly, the secretogogue(s) from the small or large intestine may be very labile, and lose its function upon being removed from its normal circulation in the thoracic duct. Lastly, the secretogogue(s) from the retained small or large intestine is a weak stimulator when acting alone; it acts to potentiate and/or stimulate the antral gastrin mechanism to produce gastric hypersecretion following massive small intestinal resection.

The findings of this study suggest that the production of gastric secretogogue(s) from the retained intestine is a more likely factor than the loss of gastric inhibitor(s) in the mechanism of gastric hypersecretion following massive small intestinal resection.

CONCLUSIONS

1. Massive small intestinal resection induces marked hypersecretion in Heidenhain pouch dogs.
2. Antrectomy before or after enterectomy can prevent or markedly reduce this hypersecretion.
3. Enterectomy is unable to bring forth hypersecretion in antrectomised dogs, but it can still lead to a significantly higher Heidenhain pouch secretion in comparison with the antrectomised phase.
4. Lymph diversion by supradiaphragmatic thoracic duct cannulation can markedly decrease Heidenhain pouch secretion in enterectomised dogs.
5. On reinfusion of diverted lymph, a return of Heidenhain pouch secretion to the level of before lymph diversion can only take place in dogs with an intact antral function.
6. Reinfusion of diverted lymph has no effect on the Heidenhain pouch secretion in antrectomised and enterectomised dogs.
7. Based on the above observations, the author postulates that:
   A. An intact antrum is essential for the production of hypersecretion after massive small intestinal resection. An antral factor, probably gastrin, is involved as the immediate stimulus for the hypersecretion.
   B. Massive small intestinal resection induces the secretion of a certain secretogogue(s) from the retained small and/or large intestine. This secretogogue(s) is likely to be carried in the thoracic duct lymph.

C. This secretogogue(s) is perhaps itself a weak stimulator which may act to potentiate and/or stimulate the antral gastrin mechanism in producing gastric hypersecretion following massive resection of the small intestine.

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APPENDIX I

MEAN HEIDENHAIN POUCH SECRETION AT DIFFERENT STAGES OF GROUP A DOGS+

	Control Period	Sham Enterectomy	Enterectomy	Antrectomy	Thoracotomy§	Lymph Diversion¶	Lymph Reinfusion¶
24-Hour Fasting							
Volume*	11.4	11.0	12.2	5.6			
Free Acid†	0.4	0.3	0.3	0			
Total Acid†	6.0	6.0	7.4	2.0			
24-Hour Post-Prandial							
Volume	40.2	39.1	67.7	16.8			
Free Acid	46.2	42.5	99.1	24.8			
Total Acid	65.0	60.8	115.2	50.4			
6-Hour Fasting							
Volume	3.88	2.1	2.7	1.7			
Free Acid	16.00	2.5	42.6	0			
Total Acid	58.20	53.1	101.4	19.6			
6-Hour Post-Prandial							
Volume	8.9	7.5	18.5	3.5	3.4	0.27	0.51
Free Acid	168.8	142.9	421.9	13.1	14.6	0	0
Total Acid	278.0	258.9	527.9	86.0	98.2	1.40	4.10

* Volume in ml.
† Acid in mEq./L.
+ Dogs included in this group were E806, E807, E945, E973, E1102, E1125, E1184.
§ During thoracotomy only the 6-hour post-prandial Heidenhain pouch secretion was performed.
¶ During the 6-hour post-prandial Heidenhain pouch secretion with lymph diversion and reinfusion, the first 3 hours were for lymph diversion whereas the last 3 hours for lymph reinfusion. Thus, the data for Heidenhain pouch secretion in lymph diversion and lymph reinfusion was mean 3-hour secretion.

APPENDIX II

MEAN HEIDENHAIN POUCH SECRETION AT DIFFERENT STAGES

OF GROUP B DOGS+

	Control Period	Antrectomy	Enterectomy	Lymph Diversion¶	Lymph Reinfusion¶
24-Hour Fasting					
Volume*	27.50	23.00	19.10		
Free Acid†	13.65	0.85	2.50		
Total Acid†	27.25	9.60	17.95		
24-Hour Post-Prandial					
Volume	139.8	32.70	41.15		
Free Acid	93.0	16.45	38.90		
Total Acid	113.8	31.65	57.70		
6-Hour Fasting					
Volume	10.1	5.9	6.6		
Free Acid	58.0	17.8	58.3		
Total Acid	131.0	54.3	127.9		
6-Hour Post-Prandial					
Volume	25.75	9.2	13.8	0.43	0.20
Free Acid	390.30	42.2	188.1	13.30	0
Total Acid	494.78	98.2	300.6	22.17	0

* Volume in ml.
† Acid in mEq./L.
+ Dogs included in this group were E68, E87, E216, E234, E419, E470, E885, E940, E1072, E1113.
¶ During the 6-hour post-prandial Heidenhain pouch secretion with lymph diversion and reinfusion, the first 3 hours were for lymph diversion whereas the last 3 hours for lymph reinfusion. Thus, the data for Heidenhain pouch secretion in lymph diversion and lymph reinfusion was mean 3-hour secretion.

APPENDIX III

MEAN HEIDENHAIN POUCH SECRETION AT DIFFERENT STAGES OF GROUP B DOGS+ WHICH UNDERWENT SHAM OPERATIONS

	Control Period	Antrectomy	Sham Enterectomy	Enterectomy	Thoracotomy§	Lymph Diversion¶	Lymph Reinfusion¶
24-Hour Fasting							
Volume*	20.5	15.0	15.0	18.5			
Free Acid†	10.2	0	0	0			
Total Acid†	15.2	3.5	1.5	10.2			
24-Hour Post-Prandial							
Volume	57.5	28.2	27.2	40.0			
Free Acid	54.0	11.0	13.0	22.2			
Total Acid	80.7	28.0	29.0	49.7			
6-Hour Fasting							
Volume	2.7	2.6	1.7	3.1			
Free Acid	33.0	0	0	2.2			
Total Acid	93.9	22.9	19.9	67.5			
6-Hour Post-Prandial							
Volume	15.8	3.9	4.4	9.5	9.6	0.25	0.14
Free Acid	279.4	0	0	227.6	206.1	0	0
Total Acid	408.8	55.2	64.9	348.6	344.8	1.50	0

* Volume in ml.
† Acid in mEq./L.
+ Dogs included in this group were E1072, E1113, E940, E880.
§ During thoracotomy only 6-hour post-prandial Heidenhain pouch secretion was performed.
¶ During the 6-hour post-prandial Heidenhain pouch secretion with lymph diversion and reinfusion, the first 3 hours were for lymph diversion, whereas the last 3 hours for lymph reinfusion. Thus, the data for Heidenhain pouch secretion in lymph diversion and lymph reinfusion was mean 3-hour secretion.

APPENDIX IV

MEAN HEIDENHAIN POUCH SECRETION AT DIFFERENT STAGES OF GROUP C DOGS+

	Control Period	Enterectomy	Lymph Diversion¶	Lymph Reinfusion¶
24-Hour Fasting				
Volume*	15.62	21.87		
Free Acid†	0	0		
Total Acid†	3.25	14.87		
24-Hour Post-Prandial				
Volume	24.75	55.62		
Free Acid	25.00	76.80		
Total Acid	50.25	99.50		
6-Hour Fasting				
Volume	1.6	4.70		
Free Acid	0	130.10		
Total Acid	46.2	244.20		
6-Hour Post-Prandial				
Volume	8.1	19.80	0.92	8.2
Free Acid	147.6	512.90	3.50	165.4
Total Acid	258.8	611.86	20.10	248.5

* Volume in ml.
† Acid in mEq./L.
+ Dogs included in this group were E937, E1001, E1198, E1284.
¶ During the 6-hour post-prandial Heidenhain pouch secretion with lymph diversion and reinfusion, the first 3 hours were for lymph diversion, whereas the last 3 hours for lymph reinfusion. Thus, the data for Heidenhain pouch secretion in lymph diversion and lymph reinfusion was mean 3-hour secretion.